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Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

02014324.4

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

Anmeldung Nr.:
Application no.:
Demande n°: 02014324.4

Anmeldetag:
Date of filing:
Date de dépôt: 27/06/02

Anmelder:
Applicant(s):
Demandeur(s):
Aventis Pharma Deutschland GmbH
65926 Frankfurt am Main
GERMANY

Bezeichnung der Erfindung:
Title of the invention:
Titre de l'invention:
N6-substituted adenosine analogues and their use as pharmaceutical agents

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

Staat: State: Pays:	Tag: Date: Date:	Aktenzeichen: File no. Numéro de dépôt:

Internationale Patentklassifikation:
International Patent classification:
Classification internationale des brevets:
C07H19/167, A61K31/70

Am Anmeldetag benannte Vertragstaaten:
Contracting states designated at date of filing:
Etats contractants désignés lors du depôt: AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE/TR

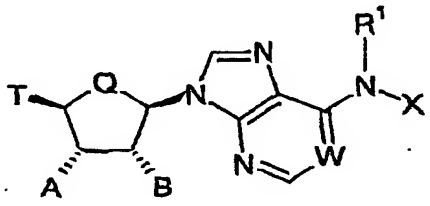
Bemerkungen:
Remarks:
Remarques:
SEE PAGE 1 OF THE DESCRIPTION FOR THE ORIGINAL TITLE.

Aventis Pharma Deutschland GmbH

27. Juni 2002
APD61988EP IB/AEW/rg

Novel adenosine analogues and their use as pharmaceutical agents

The present invention relates to compounds derived from adenosine and analogues thereof according to the general formula (I), with the definitions of R^1, A, B, Q, T, W and X given below in the text, and their use as pharmaceutical agents.



(I)

The invention furthermore relates to intermediates of compounds according to the general formula (III), as defined in the specification.

The physiological and pharmacological actions of adenosine and analogues are mediated through specific receptors located on cell surfaces. Four adenosine receptor subtypes, designated as A_1, A_{2A}, A_{2B}, and A_3 receptors, have been identified. Several potent metabolically-stable analogues of adenosine have been synthesized which demonstrate varying degrees of selectivity for the receptor subtypes.

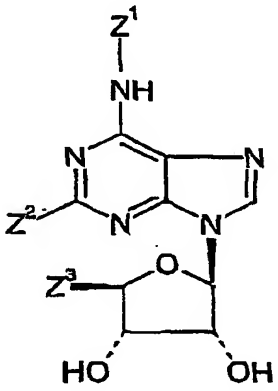
There exists are huge number of adenosine analogues having a wide variety of physiological and pharmacological actions including a marked alteration of cardiovascular, renal and fat cell function.

For example, adenosine derivatives useful as anti-hypertensive, cardioprotective, anti-ischemic and antilipolytic agents are known from US-A 5,561,134, WO 98/01426 and

WO 00/23447. Such adenosine derivatives do not have any substituents, which contain halogen and are attached to the tetrahydrofuran or cyclopentane fragments, respectively, in contrast to compounds according to the present invention.

Adenosine derivatives having substituents containing halogen and said substituents being attached to the tetrahydrofuran fragments according to the general formula (II) are disclosed by WO 99/24449 and WO 99/24450.

Said compounds can be employed, for instance, as inhibitors of lipolysis, as cardioprotective agents or they may be of value in the therapy of diabetes.



(II)

Unless indicated otherwise, the substituents of the above formula are defined for both WO 99/24449 and WO 99/24450 as follows:

Besides three further alternatives (4-6) which will not be specified below, Z^1 represents a group selected from

(1) -(alk)$_n$-(C_{3-7})cycloalkyl, including bridged cycloalkyl, said cycloalkyl group being optionally substituted by one or more substituents selected from OH, halogen, -(C_{1-3})alkoxy, wherein (alk) represents C_{1-3}alkylene and n represents 0 or 1.

(2) an aliphatic heterocyclic group of 4 to 6 membered rings containing at least one heteroatom selected from O, N or S, optionally substituted by one or more substituents selected from the group consisting of -(C_{1-3})alkyl, -CO_2-(C_{1-4})alkyl, -CO(C_{1-3}alkyl), -S(=O)$_n$-(C_{1-3}alkyl), -$CONR^aR^b$ (wherein R^a and R^b independently represent H or C_{1-3}alkyl) or =O; where there is a sulfur atom in the heterocycling ring, said sulfur is optionally substituted by (=O)$_n$, where n is 1 or 2.

(3) Straight or branched C_{1-12} alkyl, optionally including one or more O, S(=O)$_n$ (where n is 0, 1 or 2) or N groups substituted within the alkyl chain, said alkyl optionally substituted by one or more of the following groups, phenyl, halogen, hydroxy or NR^aR^b wherein R^a and R^b both represent C_{1-3}alkyl or hydrogen.

Z^2 represents C_{1-3}-alkyl, halogen or hydrogen;

Z^3 represents a fluorinated straight or branched alkyl group of 1-6 carbon atoms (in the case of WO 99/24449) or said fluorinated alkyl group is attached to the furan fragment by an -OCH_2-linker (in the case of WO 99/24450);

Referring to the definitions of Z^1 to Z^3, it is further stated in WO 99/24449 and WO 99/24450 that:

Conveniently, Z^1 may represent (alk)$_n$-C_{3-6}-cycloalkyl wherein n is 0 or 1 and the said cycloalkyl is either substituted by at least one substituent selected from halogen, particularly fluorine, and OH, or is unsubstituted. Preferably n is zero. More preferably, the cycloalkyl group is monosubstituted with either OH or fluorine and more preferably the cycloalkyl ring has 5 carbon members.

Alternatively Z^1 may represent a substituted or unsubstituted aliphatic heterocyclic group, the substitutent being selected from the group consisting of –CO_2–(C_{1-4})alkyl, -CO-(C_{1-3})alkyl, -S(=O)$_n$-(C_{1-3})alkyl, $CONR^aR^b$ and when there is a heteroatom S in the ring this heteroatom may optionally be substituted by (=O)$_n$ where n is 1 or 2. More preferably the heterocyclic ring is unsubstituted or the substituents are –CO_2-(C_{1-4})alkyl, or

when the heteroatom is S, the substituent $(=O)_n$ is attached to the heterocyclic sulfur atom. More preferably in the case of WO 99/24450, when there is a sulfur heteroatom in the ring this S is unsubstituted.

Conveniently, the aliphatic heterocyclic groups is unsubstituted or when the substituent is $-CO_2(C_{1-4})$alkyl, the heteroatom is N and the substituent is directly attached to said ring nitrogen atom.

Preferably the heterocyclic ring is 6 membered and more preferably contains only one O, N or S heteroatom.

Alternatively, Z^1 may represent a straight or branched alkyl of 1-6 carbon atoms (WO 99/24449) or 1-5 carbon atoms (WO 99/24450) optionally with at least one $S(=O)_n$ and/or N substituted in the chain, where there is an $S(=O)_n$ in the chain, preferably n is 1 or 2. The alkyl group conveniently may be unsubstituted or substituted by at least one OH group.

Z^2 preferably represents hydrogen, methyl or halogen, more preferably hydrogen, chlorine or (just for WO 99/24450) methyl.

Z^3 preferably represents a C_{1-3} fluoroalkyl group especially a fluoromethyl or (just for WO 99/24449) fluoroethyl group, more preferably $F_2C(Me)$-, FCH_2- (WO 99/24449) or F_3C- (WO 99/24450).

As examples, 5'deoxy-5'-fluoro-N-(2S-hydroxy-cyclopent-(S)-yl)-adenosine and 5'-deoxy-5'-fluoro-N-(2,2-dimethyl-propyl)-adenosine are provided by WO 99/24449 and N-(2-pyridin-4-yl-ethyl)-5'-O-trifluoromethyl-adenosine, N-(2S-fluoro-cyclopent-(S)-yl)-5'-O-trifluoromethyl-adenosine, N-tert-butyl-5'-O-trifluoromethyl-adenosine, N-(2S-hydroxy-cyclopent-(S)-yl)-5'-O-trifluoromethyl-adenosine, N-(rel-2,3-dihydroxy-propyl)-5'-O-trifluoromethyl-adenosine, N-cyclopentyl-5'-O-(2,2,2-trifluoro-ethyl)adenosine and N-(2R-hydroxy-cyclopent-(R)-yl)-5'-O-(2,2,2-trifluoro-ethyl)-adenosine by WO 99/24450.

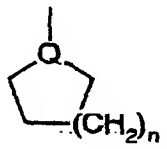
Compounds explicitly disclosed by WO 99/24449 or WO 99/24450 are as such not an object of the present invention.

WO 95/07921 discloses adenosine derivates according to the general formula (II) wherein Z^2 is halogen, amino, perhalomethyl, cyano, C_{1-6}-alkoxy, C_{1-6}-alkylthio or C_{1-6}-alkylamino. These compounds can be used for treating central nervous system ailments.

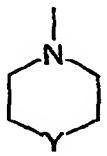
WO 97/33591 discloses the use of adenosine derivatives according to the general formula (II) for treating disorders related to cytokines in humans including autoimmune disorders, inflammation, arthritis, type I or type II diabetes, multiple sclerosis, stroke, osteoporosis, septic shock or menstrual complications.

According to WO 97/33591, compounds of the general formula (II) are defined as follows:

Z^1 is selected from the groups consisting of

(a) 

wherein Q is nitrogen or carbon, n is 1 to 3 and where the group (a) my be optionally substituted with one or two C_{1-6}-alkyl groups, C_{2-6}-alkenyl, C_{2-6}-alkynyl, phenoxy, phenylsulphonyl, phenylthio, hydroxy, phenyl, C_{1-6}-alkoxy or C_{1-6}-alkoxy, C_{1-6}-alkyl, phenylthioalkyl or

(b) 

wherein Y is O, S or NZ^4, where Z^4 is H, C_{1-6}-alkyl or phenyl, and where the group (b) may be optionally substituted with C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, phenoxy, phenyl, C_{1-6}-alkoxy or C_{1-6}-alkoxy-C_{1-6}-alkyl, or

Z^1 is $-NR^2R^3$ or $-YR^4$,
wherein Y is oxygen;
R^2 is C_{1-6}-alkyl;
R^3 is phenyl or C_{1-6}-alkyl which may be substituted by phenyl or phenoxy;
R^4 is straight-chain C_{1-6}-alkyl, branched C_{3-8}-alkyl, C_{2-8}-alkenyl or C_{3-8}-cycloalkyl, which may be substituted by phenyl or phenoxy which in turn may be substituted with nitro, halogen or amine;

Z^2 represents hydrogen, halogen, amino, perhalomethyl, cyano, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, C_{1-6}-alkylamino or phenyl;

Z^3 is hydroxymethyl, methyl, chloromethyl, bromomethyl, fluoromethyl, cyanomethyl, aminomethyl, vinyl, methylthiomethyl or methoxymethyl.

Preferably Z^1 is $-OR^4$, wherein R^4 is straight-chain C_{1-6}-alkyl, branched C_{3-8}-alkenyl or C_{3-8}-cycloalkyl, which may be substituted by phenyl or phenoxy which in turn may be substituted with nitro, halogen or amine.

Thus, compounds of the general formula (I) according to the present invention are not explicitly disclosed by WO 97/33591. Compounds explicitly disclosed by WO 97/33591 are as such not object of the present invention.

Aspects of the pathophysiology of insulin resistance and type 2 diabetes:

Insulin resistance, which is defined as a state of reduced responsiveness to normal circulating concentrations of insulin, is a characteristic trait of type 2 diabetes and contributes to abnormalities in muscle, fat tissue and liver. Insulin resistance preceds the

onset of type 2 diabetes, which develops when additional defects exist at the level of the pancreatic beta-cell. As long as the peripheral insulin resistance can be compensated by increased insulin production glucose homeostasis is balanced. Even in the absence of type 2 diabetes, insulin resistance is a key feature of other human disease states. Impaired insulin action coupled with hyperinsulinemia leads to a variety of abnormalities, including elevated triglycerides, low levels of HDL (high density lipoproteins), enhanced secretion of VLDL (very low density lipoproteins), disorders of coagulation, increased vascular resistance, changes in steroid hormone levels, attenuation of peripheral blood flow and weight gain. Thus, insulin resistance is often associated with central obesity, hypertension, polycystic ovarian syndrome, dyslipidemia, and atherosclerosis (JCI 106, 163-164, 2000).

Insulin resistance is characterized in the adipose tissue by increased lipolysis, which results in increased levels of free fatty acids, which by themselves contribute to reduced glucose utilisation in the muscle, to increased flux of fatty acids to the liver, with subsequent increased VLDL production, and to impairment of insulin secretion from the beta-cell; in the liver by increased hepatic glucose production, and VLDL secretion, which result in hyperglycemia and hypertriglyceridemia, respectively; in the muscle by reduced glucose utilisation rates, which contribute to hyperglycemia.

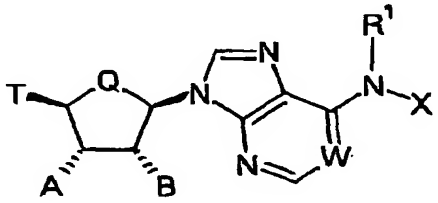
Inhibition of peripheral lipolysis by adenosine A1 receptor agonists result in reduction of plasma free fatty acids (primary pharmacological effect). Reduced availability of free fatty acids to the muscle increases glucose utilisation and reduces VLDL production in the liver which is paralleld by reduced plasma triglycerides (secondary pharmacological effect).

Thus, there exists a strong need for compounds which can be employed for the treatment of insulin resistance and type 2 diabetes. The object of the present invention is to provide compounds showing this ability.

This object is attained by a class of metabolically stable adenosine analogues, and derivatives thereof, possessing unexpectedly desirable pharmacological properties, i.e. they are antilipolytic agents having a unique therapeutic profile, fat cell specific and devoid of

direct cardio-chronotropic activity. Due to the compounds' specific activity on antilipolysis and the thereby obtained reduction of plasma lipids (e.g. free fatty acids and triglycerides), the compounds reduce both cardiovascular and metabolic risk factors and could also be useful for the treatment of cardiovascular diseases.

Therefore, this invention relates to adenosine analogues according to the general formula (I)



(I)

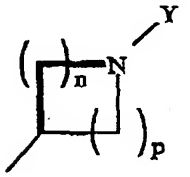
wherein:

W is N, N → O, or CH;

Q is CH_2 or O;

R^1 is selected from the group consisting of hydrogen, C_1-C_{10}-alkyl, allyl, 2-methylallyl, 2-butenyl and C_1-C_{10}-cycloalkyl;

X is selected from the group consisting of



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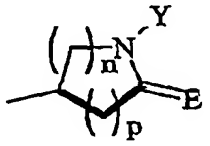


;

wherein n and p are independently 0, 1, 2, or 3, provided that n + p is at least 1;

and unsubstituted and at least monosubstituted C_1-C_{10}-alkylene-Y, C_1-C_{10}-alkenylene-Y, C_3-C_{10}-cycloalkylene-Y and C_3-C_{10}-cycloalkenylene-Y, the substituents of which are

selected from the group consisting of halogens, pseudohalogens, CF_3, C_1-C_6-alkyl and C_1-C_6-alkoxy;

E is O or S;

Y is selected from the group consisting of hydrogen; and unsubstituted and at least monosubstituted C_1-C_{10}-alkyl, aryl, heterocyclyl, aryl-(C_1-C_{10}-alkylene)- and heterocyclyl-(C_1-C_{10}-alkylene), the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, aryl, heterocyclyl, C_1-C_6-alkoxy, NH_2, (C_1-C_6-alkyl)amino, di(C_1-C_6-alkyl)amino, C_1-C_6-alkoxy-(C_1-C_6-alkylene)-, nitro, carboxy, carbalkoxy, carboxy-(C_1-C_6-alkylene)-, carbalkoxy-(C_1-C_6-alkylene)-, hydroxy, hydroxy-(C_1-C_6-alkylene)-, mercapto, (C_1-C_6-alkyl)thio, mercapto-(C_1-C_6-alkylene)-, C_1-C_6-alkyl substituted by at least one halogen, (C_1-C_6-alkyl)sulfonyl-, aminosulfonyl-, (C_1-C_6-alkyl)aminosulfonyl-, (C_1-C_6-alkyl)sulfonylamido-, (C_1-C_6-alkyl)-sulfonyl-(C_1-C_6-alkylene)amino-, HO_3S-(C_1-C_6-alkylene)-, carbamoyl-(C_1-C_6-alkylene)-, (C_1-C_6-alkyl)-carbamoyl, (C_1-C_6-alkyl)-C(O)O-, (C_1-C_6-alkyl)-CO-, $-SO_3H$ and carbamoyl;

T is a residue selected from the group consisting of C_1-C_{10}-alkyl, C_1-C_{10}-cycloalkyl, aryl-(C_1-C_{10}-alkylene)- and heterocyclyl-(C_1-C_{10}-alkylene), which residues are monosubstituted by halogen or OR_2, and which residues can be optionally substituted by at least one further substituent selected from the group consisting of halogens, pseudohalogens, mercapto, NH_2, nitro, hydroxy, unsubstituted and at least monosubstituted C_1-C_6-alkyl, C_1-C_6-alkoxy, (C_1-C_6-alkyl)amino, (C_1-C_6-alkyl)thio, aryl and heterocyclyl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy and hydroxy;

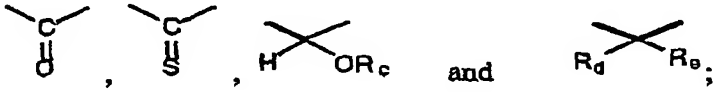
R^2 is C_1-C_{10}-alkyl substituted by at least one halogen;

A is hydrogen, C_1-C_{10}-alkyl, hydroxy-(C_1-C_{10}-alkylene)-, C_1-C_{10}-alkoxy-(C_1-C_{10}-alkylene)-, or OR';

B ist hydrogen, C_1-C_{10}-alkyl, hydroxy-(C_1-C_{10}-alkylene)-, C_1-C_{10}-alkoxy-(C_1-C_{10}-alkylene)-, or OR'';

R' and R'' are independently selected from the group consisting of hydrogen, C_1-C_6-alkyl, aryl-(C_1-C_6-alkylene)-, (C_1-C_6-alkyl)-CO, carbalkoxy, aryl-(C_1-C_6-alkylene)-CO-, and aryl-O-CO-;

when A and B are OR'and OR'', respectively, R' and R'' together may form a substituent selected from the group consisting of



R_c is hydrogen or C_1-C_6-alkyl;

R_d and R_e are independently hydrogen, C_1-C_{10}-alkyl, or together with the carbon atom to which they are attached may form a 1,1-cycloalkyl group;

heterocyclyl is a 4 to 10-membered, mono- or bicyclic heterocycle containing one or more heteroatoms selected from the group consisting of N, O and S;

aryl is phenyl, indan-1-yl, indan-2-yl, naphth-1-yl or naphth-2-yl;

or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof;

with the proviso that, in case Q is O and Y is hydrogen, X is not C_3-C_6-cycloalkylene or C_3-C_6-cycloalkylene substituted by at least one halogen; in case Q is O and Y is hydrogen, C_1-C_{10}-alkyl or C_1-C_{10}-alkyl substituted by at least one hydroxy, X is not unsubstituted C_1-C_{10}-alkylene; in case Q is O and Y-X is 2-pyridin-4-yl-ethyl, T is not CF_3OCH_2-.

As used above and throughout the description of the invention, the following terms, unless indicated otherwise, shall be understood to have the following meanings:

If, in the compounds of formula (I), groups or substituents such as, for example, aryl, heteroaryl, alkyl etc., can be present several times, they all independently from each other have the meanings indicated and can hence, in each individual case, be identical with or different from each other. One example is the di(C_1-C_6-alkyl)amino group in which the alkyl substitutents can be identical or different.

Alkyl, alkylene, alkenyl, alkenylene and alkynyl, residues can be linear or branched and are acyclic. This also applies when they are part of other groups, for example in alkoxy groups, alkoxycarbonyl groups or amino groups, or when they are substituted.

Examples for alkyl groups are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, the n-isomers of these residues, isopropyl, isobutyl, isopentyl, sec-butyl, tert-butyl, neopentyl, 3,3-dimethylbutyl. Furthermore, unless stated otherwise, the term alkyl here also includes unsubstituted alkyl residues as well as alkyl residues which are substituted by one or more, for example one, two, three or four, identical or different residues, for example aryl groups. In substituted alkyl residues, for example arylalkyl, hydroxyalkyl such as -(C_1-C_3)-alkyl-OH or alkoxyalkyl such as -(C_1-C_3)-alkyl-O-(C_1-C_4)-alkyl, the substituents can be present in any desired position.

Examples for alkenyl and alkynyl groups are the vinyl residue, the 1-propenyl residue, the 2-propenyl residue (allyl residue), the 2-butenyl residue, the 2-methyl-2-propenyl residue, the 3-methyl-2-butenyl residue, the ethynyl residue, the 2-propynyl residue (propargyl residue), the 2-butynyl residue or the 3-butynyl residue.

Examples for alkylene groups are methylene, ethylene, propylene, butylene, pentylene, hexylene, heptylene, octylene, nonylene, decylene. Furthermore, unless stated otherwise, the term alkylene here also includes unsubstituted alkylene residues as well as alkylene residues which are substituted by one or more, for example one, two, three or four, identical or different residues, for example aryl groups, the substituents can be present in any desired position.

Examples for cycloalkyl residues containing at least three carbon atoms are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. All cycloalkyl groups can be substituted by one or more identical or different (C_1-C_4)-alkyl residues, in particular by methyl. Examples for substituted cycloalkyl residues are 4-methylcyclohexyl, 4-tert-butylcyclohexyl or 2,3-dimethylcyclopentyl.

Examples for cycloalkenyl residues are cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl. All cycloalkenyl groups can be substituted by one or more identical or different (C_1-C_4)-alkyl residues, in particular by methyl.

If not stated otherwise, the above-mentioned phenyl residues, naphthyl residues and indanyl residues can be unsubstituted or can carry one or more, for example one, two, three or four, of the substituents indicated in the above definition which can be in any desired position. If in compounds of the formula (I) nitro groups are present as substituents, in total only up to two nitro groups are preferably present in the molecule. In monosubstituted phenyl residues the substituent can be in the 2-position, the 3-position or the 4-position, in disubstituted phenyl residues the substituents can be in 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position. In trisubstituted phenyl residues the substituents can be in 2,3,4-position, 2,3,5-position, 2,3,6-position, 2,4,5-position, 2,4,6-position or 3,4,5-position. In fourfold substituted phenyl residues, the substituents can be in the 2,3,4,5-position, the 2,3,4,6-position, or the 2, 3,5,6-position. Tolyl (= methylphenyl) can be 2-tolyl, 3-tolyl or 4-tolyl. Naphthyl can be 1-naphthyl or 2-naphthyl. In monosubstituted 1-naphthyl residues the substituent can be in the 2-position, the 3-position, the 4-position, the 5-position, the 6-position, the 7-position or the 8-position, in monosubstituted 2-naphthyl residues in the 1-position, the 3-position, the 4-position, the 5-position, the 6-position, the 7-position or the 8-position. In higher substituted naphthyl radicals, for example 1-naphthyl radicals or 2-naphthyl radicals which carry two or three substituents, the substituents can also be situated in all possible positions. Indanyl residues include indan-1-yl residues and indan-2-yl residues which can be unsubstituted or carry one or more of the substituents indicated. In case the indanyl residues are substituted, the substituent or substituents can be in any of the positions possible.

The above definitions as well as the following definitions relating to monovalent residues equally apply to the divalent residues phenylene, naphthylene and heteroarylene. Those divalent residues can be attached to the adjacent groups by any ring carbon atom. In the case of a phenylene residue, these can be in 1,2-position (ortho-phenylene), 1,3-position (meta-phenylene) or 1,4-position (para-phenylene). In the case of a naphthylene residue the free bonds can be in 1,2-position (= 1,2-naphthylene or 1,2-naphthalinediyl) or in 1,3-position, 1,4-position, 1,5-position, 1,6-position, 1,7-position, 1,8-position, 2,3-position, 2,6-position or 2,7-position. In the case of 5-membered ring aromatics containing one heteroatom such as, for example, thiophene or furan, the two free bonds can be in 2,3-position, 2,4-position, 2,5-position or 3,4-position. A divalent residue derived from pyridine can be a 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-pyridinediyl residue. In the case of unsymmetrical divalent residues the present invention includes all positional isomers, i. e., in the case of a 2,3-pyridinediyl residue, for example, it includes the compound in which the one adjacent group is present in the 2-position and the other adjacent group is present

in the 3-position as well as the compound in which the one adjacent group is present in the 3-position and the other adjacent group is present in the 2-position.

Unless stated otherwise, heterocyclyl residues including heteroaryl residues, heteroarylene residues and rings which are formed by two groups bonded to a nitrogen are preferably derived from heterocycles which contain one, two, three or four heteroatoms which can be identical or different; more preferably they are derived from heterocycles which contain one, two, or three, in particular one or two, heteroatoms which can be identical or different. Unless stated otherwise, the heterocycles can be monocyclic or polycyclic, for example monocyclic, bicyclic or tricyclic. Preferably they are monocyclic or bicyclic. The rings preferably are 5-membered rings, 6-membered rings or 7-membered rings. Examples of monocyclic and bicyclic heterocyclic systems from which residues occuring in the compounds of the formula (I) can be derived, are pyrrole, furan, thiophene, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, 1,3-dioxole, 1,3-oxazole (= oxazole), 1,2-oxazole (= isoxazole), 1,3-thiazole (= thiazole), 1,2-thiazole (= isothiazole), tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, pyran, thiopyran, 1,4-dioxine, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,4,5-tetrazine, azepine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, 1,3-oxazepine, 1,3-thiazepine, indole, benzothiophene, benzofuran, benzothiazole, benzimidazole, benzodioxol, quinoline, isoquinoline, cinnoline, quinazoline, quinoxaline, phthalazine, thienothiophenes, morpholinyl, 1,8-naphthyridine and other naphthyridines, pteridin, or phenothiazine, each of them in saturated form (perhydro form) such as piperidine, pyrrolidine, tetrahydrofuran or tetrahydropyran or in partially unsaturated form (for example in the dihydro form or the tetrahydro form) or in maximally unsaturated form, in case the respective forms are known and stable. The term "aryl" and the term "heteroaryl" as used herein comprise bicyclic residues in which both cycles are aromatic as well as bicyclic residues in which only one cycle is aromatic. Suitable heterocycles include, for example, the saturated heterocycles pyrrolidine, piperidine, piperazine, morpholine and thiomorpholine. The degree of saturation of heterocyclic groups is indicated in their individual definitions. Unsaturated heterocycles can contain, for example, one, two or three double bonds within the ring system. 5-membered rings and 6-membered rings can in particular also be aromatic.

Substituents which may be derived from these heterocycles can be attached via any suitable carbon atom. Residues derived from nitrogen heterocycles can carry a hydrogen atom or a substituent on a ring nitrogen atom, and examples include pyrrole, imidazole,

pyrrolidine, morpholine, piperazine residues, etc. Those nitrogen heterocyclic residues can also be attached via a ring nitrogen atom, in particular if the respective heterocyclic residue is bonded to a carbon atom. For example, a thienyl residue can be present as 2-thienyl residue or 3-thienyl residue, a furyl residue as 2-furyl residue or 3-furyl residue, a pyridyl residue as 2-pyridyl residue, 3-pyridyl residue or 4-pyridyl residue, a piperidinyl residue as 1-piperidinyl residue (= piperidino residue), 2-piperidinyl residue, 3-piperidinyl residue or 4-piperidinyl residue, a (thio)morpholinyl residue as 2-(thio)morpholinyl residue, 3-(thio)morpholinyl residue or 4-(thio)morpholinyl residue (= thiomorpholino residue). A residue derived from 1,3-thiazole or imidazole which is attached via a carbon atom can be attached via the 2-position, the 4-position or the 5-position.

In case a heterocyclic groups is substituted, it can carry one or more, for example one, two, three or four, identical or different substituents. Substituents in heterocycles can be present in any desired positions, for example in a 2-thienyl residue or 2-furyl residue in the 3-position and/or in the 4-position and/or in the 5-position, in a 3-thienyl residue or 3-furyl residue in the 2-position and/or in the 4-position and/or in the 5-position, in a 2-pyridyl residue in the 3-position and/or in the 4-position and/or in the 5-position and/or in the 6-position, in a 3-pyridyl residue in the 2-position and/or in the 4-position and/or in the 5-position and/or in the 6-position, in a 4-pyridyl residue in the 2-position and/or in the 3-position and/or in the 5-position and/or in the 6-position. Suitable nitrogen heterocycles can also be present as N-oxides or as quarternary salts containing a counterion which is derived from a pharmaceutically acceptable acid. Pyridyl residues, for example, can be present as pyridine-N-oxides.

Halogen is fluorine, chlorine, bromine oder iodine, preferably fluorine or chlorine.

Examples for pseudohalogens are CN and N_3, a preferred pseudohalogen is CN.

"Alkoxy" means an alkyl-O group in which "alkyl" is as previously described. Exemplary groups include methoxy, ethoxy, n-propoxy, i-propoxy and n-butoxy. "Carbalkoxy" means a carboxyl substituent esterified with an alcohol of the formula $C_nH_{2n+1}OH$, wherein n is from 1 to about 6.

"Prodrug" means a compound which is rapidly transformed *in vivo* to yield a compound according to formula (I), for example by hydrolysis in blood. "Pharmaceutically acceptable

prodrug" means a compound which is, within the scope of sound medical judgement, suitable for pharmaceutical use in a patient without undue toxicity, irritation, allergic response, and the like, and effective for the intended use, including a pharmaceutically acceptable ester as well as a zwitterionic form, where possible, of the peptide compounds of the invention. Pharmaceutically acceptable prodrugs according to the invention are described in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Representative solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule(s) is/are H_2O.

The compounds of Formula I contain chiral (asymmetric) centers. The invention includes the individual stereoisomers in the form of enantiomers and diastereoisomers and mixtures of the stereoisomers. The individual isomers are prepared or isolated by methods well known in the art or by methods described herein after.

The compounds described herein may be used in the form of the free base, in the form of acid addition salts or as hydrates. All such forms are within the scope of the invention. Acid addition salts are simply a more convenient form for use. In practice, use of the salt form inherently amounts to use of the base form. The acids which may be used to prepare the acid addition salts include preferably those which produce, when combined with the free base, pharmaceutically acceptable salts, that is, salts whose anions are non-toxic to the recipient in pharmaceutical doses of the salts, so that the beneficial antilipolytic effects produced by the free base are not vitiated by side effects ascribable to the anions.

Although pharamaceutically acceptable salts of the compounds of the invention are preferred, all acid addition salts are useful as sources of the free base form, even if the particular salt, per se, is desired only as an intermediate product as, for example, when the salt is formed only for purposes of purification and identification, or when it is used as an intermediate in preparing a pharmaceutically acceptable salt by ion exchange procedures. Pharmaceutically acceptable salts within the scope of the invention are those derived from the following acids: mineral acids such as hydrochloric acid, sulfuric acid, phosphoric acid, and sulfamic acid; and organic acids such as acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, fumaric acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, quinic acid and the like. The corresponding acid addition salts comprise the following: hydrochloride, sulfate, phosphate, sulfamate, acetate, citrate, lactate, tartarate, methanesulfonate, fumarate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfonate and quinate, respectively.

The acid addition salts of the compounds of the invention are conveniently prepared either by dissolving the free base in aqueous or aqueous-alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

Included within the scope of formula I are classes of compounds which may be characterized generally as N6 -substituted adenosines; N6- substituted carbocyclic adenosines (or, alternatively, dihydroxy[N6- substituted-9-adenyl]cyclopentanes) and N-oxides thereof. Also within the scope of formula I are the derivatives of compounds of the above classes in which one or both of the 2- or 3- hydroxyl groups of the cyclopentane ring or, in the cases of classes of compounds containing the ribose moiety, the 2'- or 3'-hydroxyl groups of the ribose ring are substituted. Such derivatives may themselves comprise the biologically active chemical entity useful in the treatment of insulin resistance and as antilipolytic agents, or may act as pro-drugs to such biologically active compounds which are formed therefrom under physiological conditions.

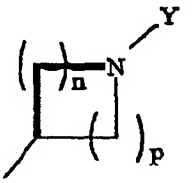
Preferred compounds of the formula (I) are those compounds in which one or more of the residues contained therein have the meanings given below, with all combinations of preferred substitutent definitions being a subject of the present invention. With respect to all preferred compounds of the formula (I) the present invention also includes all pharmaceutically acceptable salts thereof, pharmaceutically acceptable prodrugs thereof, N-oxides thereof, hydrates thereof or solvates thereof.

In preferred embodiments of the present invention, the substituents R^1, A, B, Q, T, W, X and Y of the formula (I) indepentently from each other have the following meanings. Hence, one or more of the substituents R^1, A, B, Q, T, W, X and Y can have the preferred meaning(s), the more preferred meaning(s), the even more preferred meaning(s), the much more preferred meaning(s) and/or the most preferred meaning(s) given below.

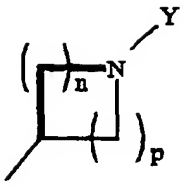
W is preferably N;

Q is preferably CH_2;

R^1 is preferably hydrogen or C_1-C_6-alkyl; R^1 is most preferably hydrogen;

X is preferably selected from the group consisting of  and unsubstituted and at least monosubstituted C_1-C_{10}-alkylene-Y and C_3-C_{10}-cycloalkylene-Y, the substituents of which are selected from the group consisting of halogens, pseudohalogens, CF_3, C_1-C_6-alkyl and C_1-C_6-alkoxy;

X is more preferably selected from the group consisting of



; and unsubstituted and at least monosubstituted C_1-C_6-alkylene-Y, the substituents of which are selected from the group consisting of CH_3, CH_3-CH_2, Cl, F, CF_3 and CH_3-O;

n + p is preferably 3 or 4;

Y is preferably selected from the group consisting of hydrogen; and unsubstituted and at least monosubstituted C_1-C_{10}-alkyl, aryl and heterocyclyl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_6-alkyl, C_1-C_6-alkoxy, NH_2, (C_1-C_6-alkyl)amino, di(C_1-C_6-alkyl)amino, C_1-C_6-alkoxy-(C_1-C_6-alkylene)-, nitro, carboxy, carbalkoxy, hydroxy, hydroxy-(C_1-C_6-alkylene)-, mercapto, (C_1-C_6-alkyl)thio, mercapto-(C_1-C_6-alkylene)-, C_1-C_6-alkyl substituted by at least one halogen, (C_1-C_6-alkyl)sulfonyl-, aminosulfonyl-; (C_1-C_6-alkyl)aminosulfonyl-, (C_1-C_6-alkyl)sulfonylamido-, SO_3H and carbamoyl;

Y is more preferably selected from the group consisting of unsubstituted and at least monosubstituted aryl and heterocyclyl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy, NH_2, (C_1-C_3-alkyl)amino, di(C_1-C_3-alkyl)amino, C_1-C_3-alkoxy-(C_1-C_3-alkylene)-, nitro, carboxy, hydroxy, hydroxy-(C_1-C_3-alkylene)-, mercapto, (C_1-C_3-alkyl)thio, mercapto-(C_1-C_3-alkylene)-, and CF_3;

Y is most preferably selected from the group consisting of unsubstituted and at least monosubstituted phenyl, pyridyl and thienyl, the substituents of which are selected from the group consisting of halogens, C_1-C_3-alkyl, C_1-C_3-alkoxy, hydroxy, mercapto and CF_3;

T is preferably C_1-C_{10}-alkyl which is monosubstituted by halogen or OR^2, and which C_1-C_{10}-alkyl can furthermore be optionally substituted by at least one substituent selected from the group consisting of halogens, pseudohalogens, mercapto, NH_2, nitro, hydroxy,

unsubstituted and at least monosubstituted C_1-C_6-alkyl, C_1-C_6-alkoxy, (C_1-C_6-alkyl)amino, (C_1-C_6-alkyl)thio, aryl and heterocyclyl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy and hydroxy;

T is more preferably C_1-C_{10}-alkyl substituted by at least one substituent selected from the group consisting of halogen and OR^2;

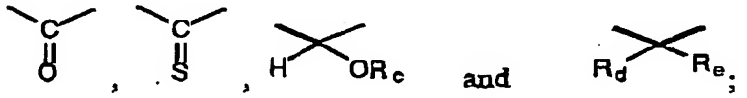
T is even more preferably C_1-C_6-alkyl substituted by at least one substituent selected from the group consisting of fluorine and OR^2;

T is much more preferably fluoromethyl, trifluoromethoxymethyl or difluoromethoxymethyl; T is most preferably fluoromethyl;

R^2 is preferably C_1-C_{10}-alkyl substituted by at least one fluorine;
R^2 is more preferably C_1-C_3-alkyl substituted by at least one fluorine;
R^2 is most preferably CF_3;

A is preferably OR';
B is preferably OR";

Preferably, R' and R'' are both hydrogen, or R' and R'' preferably together form a substituent selected from the group consisting of



R' and R" more preferably together form 

R_c is preferably hydrogen or methyl;

R_d and R_e are preferably independently hydrogen, or C_1-C_6-alkyl; R_d and R_e are more preferably both C_1-C_3-alkyl; R_d and R_e are even more preferably both methyl;

A and B are most preferably both hydroxy;

heterocyclyl is preferably selected from the group consisting of pyridyl, pyridazinyl, pyrimidinyl, isoquinolinyl, quinolinyl, quinazolinyl, imidazolyl, pyrrolyl, furanyl, thienyl, thiazolyl, benzothiazolyl, piperidinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, and morpholinyl;

heterocyclyl is more preferably selected from the group consisting of pyridyl, pyridazinyl, pyrimidinyl, imidazolyl, thienyl, thiazolyl, benzothiazolyl, piperidinyl, pyrrolidinyl, tetrahydrofuranyl, and morpholinyl;

heterocycyl is most preferably pyridyl or thienyl;

aryl is preferably phenyl, naphta-1-yl or naphtha-2-yl; aryl is most preferably phenyl.

Compounds of the formula (I) in which some or all of the above-mentioned groups have the preferred meanings, the more preferred meanings the even more preferred meanings, the much more preferred meanings or the most preferred meanings defined above are also an object of the present invention.

Most preferred compounds according to the general formula (I) are selected from the groups consisting of (1R,2S,3R,5S)-3-{6-[1-(3-chloro-phenyl-1-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl}-5-fluoromethyl-cyclopentane-1,2-diol, (1R,2S,3R,5S)-3-{6-[(R)-1-(3-chloro-thiophen-2-ylmethyl)-propylamino]-purin-9-yl}-5-fluoromethyl-cyclopentane-1,2-diol and (1R,2S,3R,5R)-3-{6-[1-(3-chloro-phenyl-1-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl}-5-trifluoromethoxymethyl-cyclopentane-1,2-diol;
or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

Compounds of this invention may be prepared by known methods or in accordance with the reaction sequences described below. The starting materials used in the preparation of compounds of the invention are known or commercially available, or can be prepared by known methods or by specific reaction schemes described herein.

The present invention also relates compounds according to the general formula (I) pharmaceutically acceptable salts thereof, pharmaceutically acceptable prodrugs thereof,

N-oxides thereof, hydrates thereof or solvates thereof, with the definitions of R^1, A, B, Q, T, W and Y given above, for use as pharmaceuticals.

Pharmaceuticals containing compounds of the formula (I), in which one or more, including all, of the above-mentioned groups have the preferred meanings, the more preferred meanings, the even more preferred meanings, the much more preferred meanings and/or the most preferred meanings defined above are also an object of the present invention.

The compounds according to the formula (I) can be used for the treatment of insulin resistance or for providing an anti-lipolytic effect. In the context of the present invention treatment includes the therapy as well as the prophylaxis of the respective deseases.

Examples of diseases which can be treated with the compounds according to the present invention include type 2 diabetes, metabolic syndrome, insulin resistance, lipid disorders such as hyper-triglyceridinia or cardiovascular disease. Preferably, compounds of the formula (I) can be employed for the treatment of type 2 diabetes or insulin resistance.

The compounds of the formula (I) and their pharmaceutically acceptable salts, optionally in combination with other pharmaceutically active compounds, can be administered to animals, preferably to mammals, and in particular to humans, as pharmaceuticals by themselves, in mixtures with one another or in the form of pharmaceutical preparations. Further subjects of the present invention therefore also are the compounds of the formula (I) and their pharmaceutically acceptable salts for use as pharmaceuticals, and in particular their use in the therapy and prophylaxis of the above-mentioned diseases and syndromes as well as their use for preparing medicaments for these purposes. Furthermore, subjects of the present invention are pharmaceutical preparations (or pharmaceutical compositions) which comprise an effective dose of at least one compound of the formula (I) and/or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, i.e. one or more pharmaceutically acceptable carrier substances and/or additives.

The amount of a compound of formula (I) which is necessary to achieve the desired biological effect depends on a number of factors, for example the specific compound

compounds modulating the energy output (e.g. ß3agonists), PPAR- and PXR-agonists and compounds which are effective on the ATP depending potassium channel of beta cells.

In one embodiment of the present invention compounds according to general formula (I) are administered in combination with an HMGCoA reductase inhibitor such as simvastatine, fluvastatine, pravastatine, lovastine, atorvastatine, cerivastatine or rosuvastatine.

In another embodiment of the present invention compounds according to a general formula (I) are advantages in combination with an inhibitor of cholesterol resorption such as ezetimibes, tiquesides or pamaquesides.

In another embodiment of the present invention compounds according to the general formula (I) are administered in combination with a PPAR gamma agonist such as rosiglitazon, pioglitazon, JTT-501 or GI 262570.

In another embodiment of the present invention compounds according to the general formula (I) are administered in combination with PPAR alpha agonists, such as GW 9578 or GW 7674.

In another embodiment of the present invention compounds according to general formula (I) are administered in combination with mixed PPAR alpha/gamma agonists such as GW 1536, AVE 8042, AVE 8134, AVE 0847, or as described in WO 00/11833, W 00/11490 and DE 101 42 734.4.

In another embodiment of the present invention compounds according to general formula (I) are administered in combination with a fibrate, such as fenofibrate, clofibrate or bezafibrate.

In another embodiment of the present invention compounds according to the general formula (I) are administered in combination with an MTP inhibitor such as implitapide, BMS-201038 or R-103757.

In another embodiment of the present invention compounds according to the general formula (I) are administered in combination with an inhibitor of colic acid resorption according to the US 6,245,744 or US 6,221,897 such as HMR 1741.

In another embodiment of the present invention compounds according to the general formula (I) are administered in combination with a CETP inhibitor, such as JTT-705.

In another embodiment of the present invention, compounds according to the general formula (I) are administered in combination with a polymeric absorber of colic acid, such as cholestyramine or colesevelam.

In another embodiment of the present invention compounds according to the general formula (I) are administered in combination with a LDL-receptor inducer according to US 6,342,512, such as HMR1171 or HMR 1586.

In another embodiment of the present invention, compounds according to a general formula (I) are administered in combination with an ACAT inhibitor, such as avasimibe.

In another embodiment of the present invention compounds according to a general formula (I) are administered in combination with an antioxidant such as OPC-14117.

(2001), 33(9), 554-558), NPY-antagonists such as naphthalin-1-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}- amide; (hydrochlorid (CGP 71683-A)) MC4-agonists such as 1-amino-1,2,3,4-tetrahydro-naphthalin-2-carboxylic acid [2-(3a-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(4-chloro-phenyl)-2-oxo-ethyl]-amide; (WO 01/91752)), orexin antagonists, such as 1-(2-methyl-benzoxazol-6-yl)-3-[1,5]naphthyridin-4-yl-urea; (hydrochloride (SB-334867-A)), H3 agonists such as 3-cyclohexyl-1-(4,4-dimethyl-1,4,6,7-tetrahydro-imidazo[4,5-c]pyridin-5-yl)-propan-1-on, oxalic acid salt (WO 00 / 63208)), TNF agonists, CRF antagonists, such as [2-methyl-9-(2,4,6-trimethyl-phenyl)-9H-1,3,9-triaza-fluoren-4-yl]-dipropyl-amine (WO 00/66585), CRF BP antagonists such as urocortin, urocortin agonists, beta 3-agonists such as 1-(4-chloro-3-methanesulfonylmethyl-phenyl)-2-[[2-(2,3-dimethyl-1-H-indol-6-yloxy)-ethylamino]-ethanol; hydrochloride (WO 01/83451), MSH (melanocyt stimulating hormone) agonists, CCK-A agonists such as {2-[4-(4-Chloro-2,5-dimethoxy-phenyl)-5-(2-cyclohexyl-ethyl)-thiazol-2-ylcarbamoyl]-5,7-dimethyl-indol-1-yl}-acetic acid trifluoroacetic acid salt (WO 99/15525), serotonin-reabsorption inhibitors, such as dexfenfluramines, mixed sertonin and noradrenergic compounds according to WO 00/71549, 5HT-agonists such as 1-(3-ethyl-benzofuran-7-yl)-piperazine oxalic acid salt (WO 01/09111), bombesine agonists, galanine antagonists, growth hormone such as human growth hormone, compounds releasing growth hormone such as 6-benzyloxy-1-(2-diisopropylamino-ethylcarbamoyl)-3,4,dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (WO 01/85695), TRH agonists according to EP 0 462 844, uncoupling protein 2 or 3 modulators, leptinagonists according to Lee, Daniel W.; Leinung, Mattew C.; Rozhavskaya-Arena, Marina; Grasso, Patricia; Leptin agonists as a potential approach to the treatment of obesity; Drugs of the Future (2001), 26 (9), 873-881, DA agonists such as bromocriptin or doprexin, lipase/amylase inhibitors according to WO 00/40569, PPAR modulators according to WO 00/78312, RXR modulators or TR agonists.

In another embodiment of the present invention compounds according to the general formula (I) are administered with the pharmaceutically active compound leptin according to e.g. "perspectives in the therapeutic use of leptin", Salvador, Javier; Gomez-Ambrosi, Javier; Fruhbeck, Gema, Expert Opinion on Pharmacotherapy (2001, 2 (10), 1615-1622.

In another embodiment of the present invention compounds according to the general formula (I) are administered in combination with the pharmaceutically active substances dexamphatamine or amphetamine.

An another embodiment of the present invention, compounds according to the general formula (I) are administered in combination with the pharmaceutically acitve substances fenfluramine or dexfenfluramine.

In another embodiment of the present invention, compounds according to the general formula (I) are administered in combination with the pharamaceutically active compound sibutramine.

In another embodiment of the present invention, compounds according to the general formula (I) are administered in combination with the pharmaceutically acitve substance orlistate.

In another embodiment of the present invention the compounds according to the general formula (I) are administered in combination with the pharmaceutically acitve substances mazindol or phentermin.

In another embodiment of the present invention, compounds according to the general formula (I) are administered in combination with bulk material, preferably insoluble bulk material (according to , e. g., Carob/Caromax® (Zunft H J; et al., Carob pulp preparation for treatment of hypercholesterolemia, ADVANCES IN THERAPY (2001 Sep-Oct), 18(5), 230-6) Caromax is a product containing carob of the company Nutrinova, Nutrition Specialties& Food Ingredients GmbH, Industriepark Höchst, 65926 Frankfurt/Main, Germany). Compounds according to the general formula I and Caromax® can be

administered either as a combination preparation or individually. Caromax® can also be adminstered as nutritions, such as within bicuits or muesli bars.

In another embodiment of the present invention, compounds according to the general formula (I) are administered in combination with at least one compound selected from the groups consisting of statins; ACE-inhibitors; AT1-antagonists; Ca-antagonists; beta-blockers; vitamins, in particular vitamin C and vitamin B6 and niacine.

Subject of the present invention are also combination preparations containing at least on compound according to a general formula (I), at least one of the pharmaceutically active substances as indicated above and additional pharmaceutically acitve substances which are not indicated above.

The pharmaceutical compositions according to the invention can be produced by one of the known pharmaceutical methods which essentially consist of mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

Besides compounds according to the invention and carriers, the pharmaceutical preparations can also contain additives, for example fillers, disintegrants, binders, lubricants, wetting agents, stabilizers, emulsifiers, dispersants, preservatives, sweeteners, colorants, flovorings, aromatizers, thickeners, diluents, buffer substances, solvents, solubilizers, agents for achieving a depot effect, salts for altering the osmotic pressure, coating agents or antioxidants.

Pharmaceutical compositions according to the invention are those suitable for oral, rectal, topical, peroral (for example sublingual) and parenteral (for example subcutaneous, intramuscular, intradermal or intravenous) administration although the most suitable mode of administration in each individual case depends on the nature and severity of the condition to be treated and on the nature of the compound of formula (I) used in each case.

Coated formulations and coated slow-release formulations also lie within the scope of the invention. Formulations resistant to acid and gastric fluid are preferred. Suitable coatings resistant to gastric fluid comprise cellulose acetate phthalate, polyvinyl acetate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

Suitable pharmaceutical compounds for oral administration may be in the form of separate units such as, for example, capsules, cachets, suckable tablets or tablets, each of which contain a defined amount of the compound of formula (I); as powders or granules; as solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. These compositions may, as already mentioned, be prepared by any suitable pharmaceutical method which includes a step in which the active ingredient and the carrier (which may consist of one or more additional ingredients) are brought into contact. In general, the compositions are produced by uniform and homogeneous mixing of the active ingredient with a liquid and/or finely divided solid carrier, after which the product is shaped if necessary. Thus, for example, a tablet can be produced by compressing or molding a powder or granules of the compound, where appropriate with one or more additional ingredients. Compressed tablets can be produced by tabletting the compound in free-flowing form, such as, for example, a powder or granules, where appropriate mixed with a binder, lubricant, inert diluent and/or a (plurality of) surface-active/dispersing agent(s) in a suitable machine. Molded tablets can be produced by molding the compound which is in powder form and is moistened with an inert liquid diluent in a suitable machine.

Pharmaceutical compositions suitable for peroral (sublingual) administration comprise suckable tablets which contain a compound of formula (I) with a flavoring, normally sucrose and gum arabic or tragacanth, and pastilles which comprise the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

Suitable pharmaceutical compositions for parenteral administration comprise preferably sterile aqueous preparations of a compound of formula (I), which are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also take place by subcutaneous, intramuscular or intradermal injection. These preparations can preferably be produced by mixing the compound with water and making the resulting solution sterile and isotonic with blood. Injectable compositions according to the invention generally contain from 0.1 to 5% by weight of the active compound.

Suitable pharmaceutical compositions for rectal administration are preferably in the form of single-dose suppositories. These can be produced by mixing a compound of formula (I) with one or more conventional solid carriers, for example cocoa butter, and shaping the resulting mixture.

Suitable pharmaceutical compositions for topical application to the skin are preferably in the form of ointment, cream, lotion, paste, spray, aerosol or oil. Carriers which can be used are petrolatum, lanolin, polyethylene glycols, alcohols and combinations of two or more of these substances. The active ingredient is generally present in a concentration of from 0.1 to 15% by weight of the composition, for example from 0.5 to 2%.

Transdermal administration is also possible. Suitable pharmaceutical compositions for transdermal uses can be in the form of single plasters which are suitable for long-term close contact with the patient's epidermis. Such plasters suitably contain the active ingredient in an optionally buffered aqueous solution, dissolved and/or dispersed in an adhesive or dispersed in a polymer. A suitable active ingredient concentration is about 1% to 35%, preferably about 3% to 15%. As a special possibility, the active ingredient can be released as described, for example, in Pharmaceutical Research, 2(6): 318 (1986) by electrotransport or iontophoresis.

Furthermore, suitable pharmaceutical compositions containing a compound of formula (I) can also be administered in fom of a pill, lacquered tablet, sugar-coated tablet, hard or soft gelatin capsule, syrup, tincture, cream, lotion, nasal spray, aerosol mixture, microcapsule, implant or rod.

The following preparations serve to illustrate the invention without restricting it, however.

Example A

Soft gelatin capsules containing 100 mg of active ingredient per capsule:

	per capsule
Active ingredient	100 mg
Triglyceride mixture fractionated from coconut fat	400 mg
Capsule contents	500 mg

Example B

Emulsion containing 60 mg of active ingredient per 5 ml:

	per 100 ml emulsion
Active ingredient	1.2 g
Neutral oil	q.s.
Sodium carboxymethylcellulose	0.6 g
Polyoxyethylene stearate	q.s.
Glycerol, pure	0.2 to 2.0 g
Flavoring	q.s.

preferred meanings, the even more preferred meanings, the much more preferred meanings and/or the most preferred meanings given below.

W is preferably N;

Q is preferably CH_2;

D is preferably chlorine or fluorine, D is most preferably chlorine;

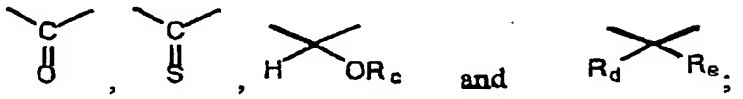
T is preferably C_1-C_{10}-alkyl which is monosubstituted by halogen or OR^2, and which C_1-C_{10}-alkyl can furthermore be optionally substituted by at least one substituent selected from the group consisting of halogens, psendohalogens, mercapto, NH_2, nitro, hydroxy, unsubstituted and at least monosubstituted C_1-C_6-alkyl, C_1-C_6-alkoxy, (C_1-C_6-alkyl)amino, aryl and heterocyclyl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy and hydroxy;

T is more preferably C_1-C_{10}-alkyl substituted by at least one substituent selected from halogens and OR^2; T is even more preferably fluoromethyl, trifluoromethoxymethyl, difluoromethoxymethyl, $CH_3SC(S)$-O-CH_2- or $CH_3S(O)_2$-O-CH_2- ;T is much more preferably fluoromethyl, trifluoromethoxymethyl or difluoromethoxymethyl; T is most preferably fluoromethyl;

A is preferably OR';

B is preferably OR'';

Preferably, R' and R'' are both hydrogen or R' and R'' together preferably form a substituent selected from the group consisting of



R' and R'' together more preferably form 

R_c is preferably hydrogen or methyl;

R_d and R_e are preferably independently hydrogen, or C_1-C_6-alkyl, R_d and R_e are more preferably both C_1-C_3-alkyl; R_d and R_e are even more preferably both methyl.

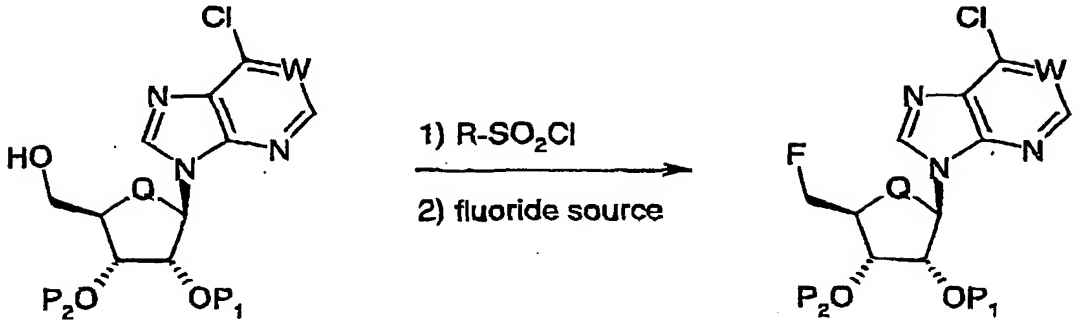
Compounds of the formula (III) in which some or all of the above-mentioned groups have the preferred meanings, the more preferred meanings or the most preferred meanings defined above are also an object of the present invention.

Most preferred compounds according to the general formula (III) are selected from the group consisting of 6-chloro-9-((3aS,4R,6S,6aR)-6-fluoromethyl-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-yl)-9H-purine, 6-fluoro-9-((3aS,4R,6S,6aR)-6-fluoromethyl-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-yl)-9H-purine, 6-chloro-9-((1R,2S,3R,5R)-5-fluoromethyl-1,2-dihydroxy-cyclopent-3-yl-)-9H-purine, 6-fluoro-9-((1R,2S,3R,5R)-5-fluoromethyl-1,2-dihydroxy-cyclopent-3-yl-)-9H-purine, 6-chloro-9-((3aS,4R,6S,6aR)-6-trifluoromethoxymethyl-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-yl)-9H-purine, 6-fluoro-9-((3aS,4R,6S,6aR)-6-trifluoromethoxymethyl-2,2-dimethyl-tetrahydrocyclo-penta-1,3-dioxol-4-yl)-9H-purine, 6-chloro-9-((1R,2S,3R,5R)-5-trifluoromethoxy-methyl-1,2-dihydroxy-cyclopent-3-yl-)-9H-purine and 6-fluoro-9-((1R,2S,3R,5R)-5-trifluoro-methoxymethyl-1,2-dihydroxy-cyclopent-3-yl-)-9H-purine, or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

Compounds of this invention may be prepared following the scheme drawn below:

Compounds of formula I, wherein W = N, Q is CH_2 and T is CH_2F are prepared starting with the product of Reaction Scheme A. In this reaction, 6-chloroaristeromycine, with the 1 and 2 hydroxyl groups of the carbocycle protected (protecting group P), is treated with a sulfonyl derivative, for example methanesulfonyl chloride, and the product sulfonate treated with a suitable fluoride source, for example tetrabutylammonium fluoride, to yield the 5-fluoromethyl derivative.

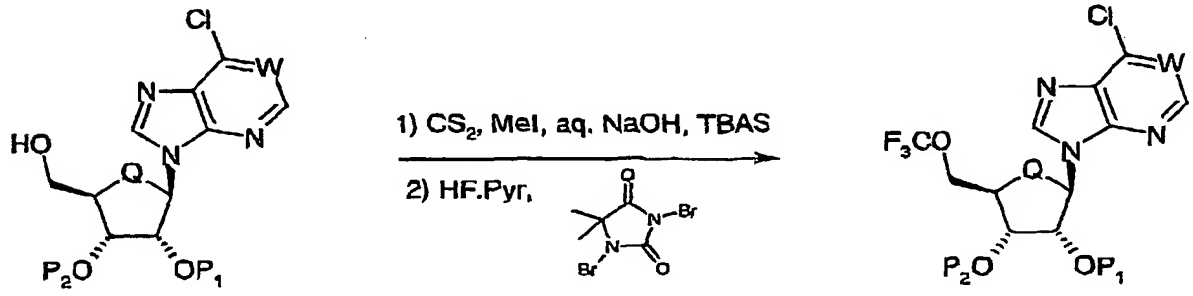
REACTION SCHEME A



(P = protecting group)

Compounds of formula I, wherein W = N, Q is CH_2 and T is CH_2OCF_3 are prepared starting with the product of Reaction Scheme B. In this reaction, 6-chloroaristeromycine, with the 1 and 2 hydroxyl groups of the carbocycle ring protected, is treated with CS_2 and an alkylating agent, for example CH_3I, in the presence of aqueous alkaline hydroxide salt, for example a 50 % solution of NaOH and a phase transfer agent, for example tetrabutylammonium hydrogensulfate, and the product thiocarbonate treated with a suitable fluoride source, for example hydrogen fluoride pyridine complex, and a suitable electrophile source, for example 1,3-dibromo-5,5-dimethyl hydantoin, to yield the 5-trifluoromethyl derivative.

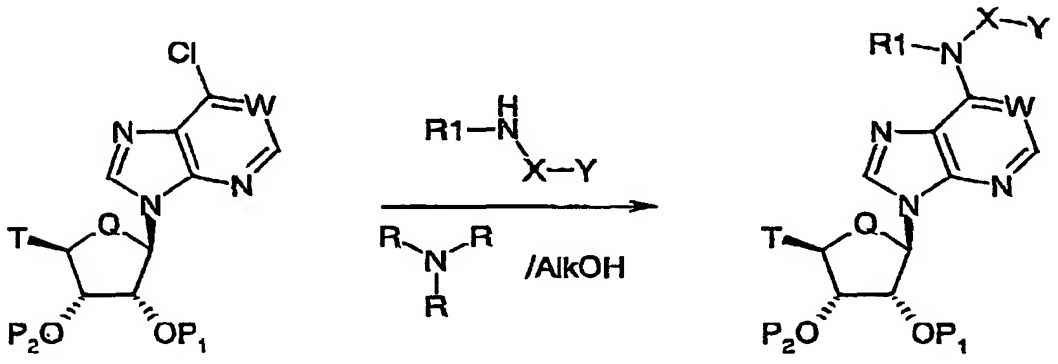
REACTION SCHEME B



(P = protecting group)

The N6-substituted adenosine and carbocyclic adenosine analogues of the invention may be formed by reacting 6-halopurine riboside or the products of Reaction Schemes A or B with various appropriate amines, as exemplified in Reaction Scheme C. 6-halopurine is preferably 6-fluoropurine or 6-chloropurine.

REACTION SCHEME C



Where X and Y are as defined hereinabove, or protected derivatives thereof.

Compounds of the present invention wherein W is N→O, i.e. the N-oxides, may be prepared by oxidation of the corresponding adenosine or carbocyclic adenosine analogue by known methods, for example by treatment with hydrogen peroxide in acetic acid.

Functional groups of starting compounds and intermediates that are used to prepare the compounds of the invention may be protected by common protecting groups (P) known in the art. Conventional protecting groups for amino and hydroxyl functional groups are described, for example, in T. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York (1984).

Hydroxyl groups may be protected as esters, such as acyl derivatives, or in the form of ethers. Hydroxyl groups on adjacent carbon atoms may advantageously be protected in the form of ketals or acetals. In practice, the adjacent 1 and 2 hydroxyl groups of the starting compounds in Reaction Schemes A and B are conveniently protected by forming the 1,2 isopropylidene derivatives. The free hydroxyls may be restored by acid hydrolysis, for

example, or other solvolysis or hydrogenolysis reactions commonly used in organic chemistry.

Following synthesis, compounds of the invention are typically purified by medium pressure liquid chromatography (MPLC), flash chromatography or column chromatography through a silica gel or Florisil matrix, followed by crystallization. For compounds of formula I typical solvent systems include chloroform:methanol, ethyl acetate:hexane, and methylene chloride:methanol. Eluates may be crystallized from methanol, ethanol, ethyl acetate, hexane or chloroform, etc.

Compounds requiring neutralization may be neutralized with a mild base such as sodium bicarbonate, followed by washing with methylene chloride and brine. Products which are purified as oils are sometimes triturated with hexane/ethanol prior to final crystallization.

The present invention will now be illustrated and explained by the following examples.

Example 1

Preparation of (1*R*,2*S*,3*R*,5*S*)-3-{6-[1-(3-chloro-phenyl-1-yl)-pyrrolidin-3(*S*)-ylamino]-purin-9-yl}-5-fluoromethyl-cyclopentane-1,2-diol

Step 1: Prepartion of 3(*S*)-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl-pyrrolidin)-*tert*-butyloxycarbamate:

To a cold (0° C) solution of 3(*R*)-hydroxy-pyrrolidine-1-carboxylic acid, *tert*-butyl ester (5 gr, 24.03 mmoles) in THF (15 ml) was added PPh_3 (7.25 gr, 27.64 mmoles) and phtalimide (4.07 gr, 27.64 mmoles). To the resulting white suspension was added drop wise a solution of DIAD (5.73 ml, 27.64 mmoles) in THF (15 ml), and the resulting yellow solution was warmed up to room temperature and stirred for 17 hours. The solution was then treated with water (30 ml) and 100 ml of a saturated aqueous solution of K_2CO_3, the aqueous layer was separated and extracted two times with EtOAc. The combined organic layers are washed with brine and dried over magnesium sulfate. The filtrate is concentrated under reduced pressure to give a residue which is purified by flash

chromatography on silica gel eluting with 25 % to 35 % EtOAc in cyclohexane to yield 3(*S*)-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl-pyrrolidin)-*tert*-butyloxycarbamate as a white solid.

Step 2: 3(*S*)-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pyrrolidine hydrochloride

3(*S*)-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl-pyrrolidin)-*tert*-butyloxycarbamate (6.2 gr, 17.64 mmoles) was dissolved in a 4 M solution of HCl in dioxane (60 ml) and the suspension was stirred 2 hours at room temperature. Et_2O was added, the solid was collected by filtration, washed 4 times with Et_2O and dried under vacuum to yield 3(*S*)-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pyrrolidine hydrochloride as a white solid.

Step 3: 3(*S*)-3-[1-(3-chlorophenyl)-pyrrolidin-3-yl]-isoindol-1,3-dione

3(*S*)-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pyrrolidine hydrochloride (500 mg, 1.98 mmoles), NEt_3 (833 µl, 5.94 mmoles), 3-chlorophenyl-boronic acid (638 mg, 3.96 mmoles) and $Cu(OAc)_2$ (359 mg, 1.98 mmoles) were combined in CH_2Cl_2 (11 ml) and the blue suspension was stirred at air for 17 hours. The green suspension was then treated with a saturated aqueous solution of NH_4Cl (30 ml), the aqueous layer was separated and extracted three times with EtOAc. The combined organic layers were washed with a saturated aqueous solution of NH_4Cl and dried over magnesium sulfate. The filtrate was concentrated under reduced pressure to give a residue which was purified by flash chromatography on silica gel eluting with 22 % EtOAc in cyclohexane to yield 3(*S*)-3-[1-(3-chlorophenyl)-pyrrolidin-3-yl]-isoindol-1,3-dione as a yellow oil.

Step 4: Preparation of 1-(3-Chloro-phenyl)-pyrrolidin-3(*S*)-ylamine hydrochloride

3(*S*)-3-[1-(3-chlorophenyl)-pyrrolidin-3-yl]-isoindol-1,3-dione (630 mg, 1.74 mmoles) and hydrazine hydrate (252 µl, 5.21 mmoles) were combined in EtOH (25 ml) and heated to reflux for 3 hours. The suspension was then cooled to room temperature, the solid was filtered off, washed 3 times with EtOH, the filtrate was evaporated to dryness, partitioned between aqueous 1N HCl (10 ml), water (30 ml) and EtOAc, the aqueous layer was separated and extracted three times with EtOAc, made alkaline with 5N aqueous NaOH, extracted three times with EtOAc and the basic extract was washed with brine and dried over magnesium sulfate. The filtrate was concentrated under reduced pressure to give

a residue which was taken up in 10 ml of a 4N HCl solution in dioxane and Et_2O (10 ml); the solution was evaporated to dryness and the residue dried under vacuum to yield 1-(3-Chloro-phenyl)-pyrrolidin-3(*S*)-ylamine hydrochloride as a brown foam.

Step 5: Preparation of methanesulfonic acid (3a*R*,4*R*,6*R*,6a*S*)-6-(6-chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-ylmethyl ester

6-Chloroaristeromycine acetonide (324 mg, 1 mmole) is dissolved in 8 ml of pyrdine, the solution is cooled to 0° C and methanesulfonyl chloride (120 µl, 1.5 mmoles) was added dropwise. The reaction mixture was then stirred for 1 hour at 0° C, allowed to warm to room temperature and the suspension was stirred vigorously for 1 hour. The solvent was then evaporated to dryness and the residue was partitioned between water and EtOAc, the aqueous layer was separated and extracted twice with EtOAc. The combined organic layers were washed with brine and dried over magnesium sulfate. The filtrate was concentrated under reduced pressure to yield methanesulfonic acid (3a*R*,4*R*,6*R*,6a*S*)-6-(6-chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-ylmethyl ester as a yellow oily residue, used directly in the next step.

Step 6: Preparation of 6-chloro-9-((3a*S*,4*R*,6*S*,6a*R*)-6-fluoromethyl-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-yl)-9H-purine

Methanesulfonic acid (3a*R*,4*R*,6*R*,6a*S*)-6-(6-chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-ylmethyl ester (402 mg, 1 mmole) prepared as described above and tetrabutylammonium fluoride (hereafter TBAF) as a 1M solution in THF (3 ml, 3 mmoles) are combined in THF (10 ml) and the brown solution was stirred overnight at room temperature. The solvent was then evaporated to dryness and the residue was partitioned between water and EtOAc, the aqueous layer was separated and extracted twice with EtOAc. The combined organic layers were washed with brine and dried over magnesium sulfate. The filtrate was concentrated under reduced pressure to give a residue which is purified by flash chromatography on silica gel eluting with 40 % EtOAc in cyclohexane to yield 6-chloro-9-((3a*S*,4*R*,6*S*,6a*R*)-6-fluoromethyl-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-yl)-9H-purine together with 6-fluoro-9-((3a*S*,4*R*,6*S*,6a*R*)-6-fluoromethyl-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-yl)-9H-purine as an approximately 1 to 1 mixture of compounds, used as such in the next step.

Step 7: Preparation of [(*S*)-1-(3-chloro-phenyl)-pyrrolidin-3-yl]-[9-((3a*S*,4*R*,6*S*,6a*R*)-6-fluoromethyl-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-yl)-9H-purin-6-yl]-amine

1-(3-Chloro-phenyl)-pyrrolidin-3(*S*)-ylamine hydrochloride (300 mg, 1.29 mmol s) prepared as in step 4 of example 1 and 6-chloro-9-((3a*S*,4*R*,6*S*,6a*R*)-6-fluoromethyl-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-yl)-9H-purine (420 mg, 1.29 mmoles) prepared as described above were combined in EtOH (12 ml), NEt_3 (730 µl, 5.15 mmoles) was then added and the resulting brown solution was stirred at reflux under an argon atmosphere. After 22 h, the reaction mixture was cooled to room temperature, evaporated to dryness, the residue was partitioned between water and EtOAc, the aqueous layer was separated and extracted two times with EtOAc. The combined organic layers are washed with brine and dried over magnesium sulfate. The filtrate is concentrated under reduced pressure to give a residue which is purified by flash chromatography on silica gel eluting with 40 % EtOAc in cyclohexane followed by 5 % MeOH in CH_2Cl_2 to yield [(*S*)-1-(3-chloro-phenyl)-pyrrolidin-3-yl]-[9-((3a*S*,4*R*,6*S*,6a*R*)-6-fluoromethyl-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-yl)-9H-purin-6-yl]-amine

Step 8: (1*R*,2*S*,3*R*,5*S*)-3-{6-[1-(3-chloro-phenyl-1-yl)-pyrrolidin-3(*S*)-ylamino]-purin-9-yl}-5-fluoromethyl-cyclopentane-1,2-diol

[(*S*)-1-(3-chloro-phenyl)-pyrrolidin-3-yl]-[9-((3a*S*,4*R*,6*S*,6a*R*)-6-fluoromethyl-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-yl)-9H-purin-6-yl]-amine (250 mg, 0.5 mmole) prepared as described above was put in solution in THF (8 ml) and the resulting solution was treated with 12 N HCl in water (500 µl, 6 mmoles), and stirred for 2 h at room temperature. The solvent was then evaporated to dryness and the residue was dried under vacuum to yield (1*R*,2*S*,3*R*,5*S*)-3-{6-[1-(3-chloro-phenyl-1-yl)-pyrrolidin-3(*S*)-ylamino]-purin-9-yl}-5-fluoromethyl-cyclopentane-1,2-diol as its dihydrochloride salt. ^1H NMR (400 MHz, $(CD_3)_2SO$ d6, at 353K, δ in ppm) : from 1.75 to 1.95 (mt : 1H) ; from 2.15 to 2.55 (mt : 4H) ; from 3.30 to 3.50 (mt : 2H) ; 3.54 (mt : 1H) ; 3.73 (dd, J = 10 and 6.5 Hz : 1H) ; 3.96 (mt : 1H) ; 4.38 (dd, J = 9 and 6 Hz : 1H) ; 4.56 (d mt, J_{HF} = 47.5 Hz ; 2H) ; 4.86 (mt : 1H) ; 5.18 (mf : 1H) ; 6.54 (large d, J = 8 Hz : 1H) ; 6.57 (large s: 1H) ; 6.65 (large d, J = 8 Hz ; 1H) ; 7.18 (t, J = 8 Hz : 1H) ; 8.47 (s : 1H) ; 8.63 (s : 1H) ; from 9.10 to 9.50 (mf : 1H).

Example 2:

Preparation of (1*R*,2*S*,3*R*,5*S*)-3-{6-[(*R*)-1-(3-chloro-thiophen-2-ylmethyl)-propylamino]-purin-9-yl}-5-fluoromethyl-cyclopentane-1,2-diol:

Step 1: Preparation of [(*R*)-1-(3-chloro-thiophen-2-ylmethyl)-propyl]-[9-((3a*S*,4*R*,6*S*,6a*R*)-6-fluoromethyl-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-yl)-9H-purin-6-yl]-amine

(*R*)-1-(3-Chloro-thiophen-2-ylmethyl)-propylamine hydrochloride (1.36 g, 6 mmoles) and 6-chloro-9-((3a*S*,4*R*,6*S*,6a*R*)-6-fluoromethyl-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-yl)-9H-purine (1.63 g, 5 mmoles) prepared as described above were combined in nBuOH (40 ml), $^{i}Pr_2NEt$ (3.5 ml, 20 mmoles) was then added and the resulting solution was stirred at reflux under an argon atmosphere. After 5 h, the reaction mixture was cooled down to room temperature, partitioned between water, brine and EtOAc, the aqueous layer was separated and extracted two times with EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. The filtrate is concentrated under reduced pressure to give a residue which was purified by flash chromatography on silica gel eluting with 2 % MeOH in CH_2Cl_2 to yield [(*R*)-1-(3-chloro-thiophen-2-ylmethyl)-propyl]-[9-((3a*S*,4*R*,6*S*,6a*R*)-6-fluoromethyl-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-yl)-9H-purin-6-yl]-amine

Step 2: (1*R*,2*S*,3*R*,5*S*)-3-{6-[(*R*)-1-(3-chloro-thiophen-2-ylmethyl)-propylamino]-purin-9-yl}-5-fluoromethyl-cyclopentane-1,2-diol:

[(*R*)-1-(3-chloro-thiophen-2-ylmethyl)-propyl]-[9-((3a*S*,4*R*,6*S*,6a*R*)-6-fluoromethyl-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-yl)-9H-purin-6-yl]-amine (1.23 g, 2.56 mmoles) prepared as described above was put in solution in THF (31 ml) and the resulting solution was treated with 12 N HCl in water (2.56 ml, 30.7 mmoles), and stirred for 2 h at room temperature. The solvent was then evaporated to dryness and the residue partitioned between water and AcOEt and neutralized with a saturated bicarbonate solution, the aqueous layer was separated and extracted twice with EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. The filtrate was concentrated under reduced pressure to give a residue which was taken up in $^{i}Pr_2O$ and the

resulting solution is diluted with pentane, the solid was filtrated, washed with pentane 3 times and dried to yield (1*R*,2*S*,3*R*,5*S*)-3-{6-[(*R*)-1-(3-chloro-thiophen-2-ylmethyl)-propylamino]-purin-9-yl}-5-fluoromethyl-cyclopentane-1,2-diol. ^{1}H NMR (300 MHz, $(CD_3)_2SO$ d6, δ in ppm) : 0.92 (t, J = 7,5 Hz : 3H) ; 1.68 (mt : 2H) ; 1.84 (mt : 1H) ; 2.31 (mt : 2H) ; 3.13 (mt : 2H) ; 3.92 (mt : 1H) ; 4.40 (mt : 1H) ; 4.51 (mf : 1H) ; 4.55 (d mt, J_{HF} = 48 Hz : 2H) ; 4.75 (mt : 1H) ; 4.94 (d, J = 3,5 Hz : 1H) ; 5.10 (d, J = 6 Hz : 1H) ; 6.98 (d, J = 5 Hz : 1H) ; 7.43 (d, J = 5 Hz : 1H) ; 7.72 (broad d, J = 8 Hz : 1H) ; 8.18 (mf ; 1H) ; 8.23 (s :1H). m.p. = 143°.

Example 3:

Preparation of (1*R*,2*S*,3*R*,5*R*)-3-{6-[1-(3-chloro-phenyl-1-yl)-pyrrolidin-3(*S*)-ylamino]-purin-9-yl}-5-trifluoromethoxymethyl-cyclopentane-1,2-diol

Step 1: Preparation of dithiocarbonic acid O-[(3a*R*,4*R*,6*R*,6a*S*)-6-(6-chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-ylmethyl] ester S-methyl ester:

To a solution of 6-chloroaristeromycine acetonide (1 gr, 3.08 mmoles) in toluene (12 ml) was sequentially added CS_2 (3.1 ml, 51.3 mmoles), Bu_4NHSO_3 (1.05 gr, 3.08 mmoles), MeI (211 µl, 3.39 mmoles), and NaOH (3.08 ml of a 50 % aqueous solution, 38.5 mmoles). The resulting white suspension was vigorously stired at room temperature for 90 minutes. 10 ml of toluene and 30 ml of water was then added, the aqueous layer was separated and extracted three times with EtOAc. The combined organic layers were washed with water and dried over magnesium sulfate. The filtrate was concentrated under reduced pressure to give a residue which was dried under vacuum to give dithiocarbonic acid O-[(3a*R*,4*R*,6*R*,6a*S*)-6-(6-chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-ylmethyl] ester S-methyl ester as a gummy yellow solid.

Step 2: Prepartion of (1*R*,2*S*,3*R*,5*R*)-3-(6-chloro-purin-9-yl)-5-trifluoromethoxymethyl-cyclopentane-1,2-diol

To a cooled (- 78° C) suspension of 1,3-dibromo-5,5-dimethyl hydantoin (1.26 gr, 9.24 mmoles) in CH_2Cl_2 (25 ml) was added HF x Pyridine complex (6 ml), and dithiocarbonic acid O-[(3a*R*,4*R*,6*R*,6a*S*)-6-(6-chloro-purin-9-yl)-2,2-dimethyl-tetrahydro-

cyclopenta-1,3-dioxol-4-ylmethyl] ester S-methyl ester (1.28 gr, 3.08 mmoles), prepared as described in step 1, in CH_2Cl_2 (10 ml). The resulting mixture was stirred 15 minutes at – 78° C, then warmed up to 0° C over 1 hour. The reaction mixture was then poured onto a mixture of 180 ml of a saturated aqueous solution of $NaHCO_3$ and 50 ml of a 50 % aqueous solution of Na_2SO_3, stirred for 20 minutes, then extracted 4 times with CH_2Cl_2. The combined organic layers were washed with water and dried over magnesium sulfate. The filtrate was concentrated under reduced pressure to give a residue which was purified by flash chromatography on silica gel eluting with 14 % Cyclohexane in EtOAc, followed by 10 % MeOH in CH_2Cl_2 to yield (1*R*,2*S*,3*R*,5*R*)-3-(6-chloro-purin-9-yl)-5-trifluoromethoxymethyl-cyclopentane-1,2-diol as a brown foam.

Step 3: Preparation of (1*R*,2*S*,3*R*,5*R*)-3-{6-[1-(3-chloro-phenyl-1-yl)-pyrrolidin-3(*S*)-ylamino]-purin-9-yl}-5-trifluoromethoxymethyl-cyclopentane-1,2-diol

To a solution of 1-(3-Chloro-phenyl)-pyrrolidin-3(*S*)-ylamine hydrochloride (130 mg, 0.55 mmole) prepared as in step 4 of example 1, in EtOH (14 ml) was added NEt_3 (196 µl, 1.4 mmoles), followed by (1*R*,2*S*,3*R*,5*R*)-3-(6-chloro-purin-9-yl)-5-trifluoromethoxymethyl-cyclopentane-1,2-diol prepared as above (182 mg, 0.46 mmole), and the resulting solution was stirred at reflux for 24 hours. The solvent was then evaporated to dryness and the residue partitioned between water and AcOEt. The aqueous layer was separated and extracted twice with EtOAc. The combined organic layers were washed with brine and dried over magnesium sulfate to give a residue which was purified by flash chromatography on silica gel eluting with EtOAc, followed by 8 % MeOH in CH_2Cl_2 to yield a solid which was re-purified by preparative LC-MS. The fractions containing the compound was taken up in water and $NaHCO_3$ solution and extracted twice with EtOAc. The combined organic layers were washed with brine and dried over magnesium sulfate to yield (1*R*,2*S*,3*R*,5*R*)-3-{6-[1-(3-chloro-phenyl-1-yl)-pyrrolidin-3(*S*)-ylamino]-purin-9-yl}-5-trifluoromethoxymethyl-cyclopentane-1,2-diol as a yellow oily residue. ^1H NMR (300 MHz, $(CD_3)_2SO$ d6, δ in ppm) : 1.82 (mt : 1H) ; 2.21 (mt : 1H) ; from 2.25 to 2.45 (mt : 3H) ; from 3.25 to 3.40 (mt : 2H) ; 3.48 (mt : 1H) ; 3.66 (mt : 1H) ; 3.91 (mt : 1H) ; 4.23 (mt : 2H) ; 4.43 (mt : 1H) ; 4.77 (mt : 1H) ; from 4.80 to 5.05 (broad mf : 1H) ; 5.01 (d, J = 4.5 Hz : 1H) ; 5.12 (d, J= 6 Hz : 1H) ; 6.51 (mt : 2H) ; 6.62 (broad d, J = 8 Hz : 1H) ; 7.18 (t, J = 8 Hz : 1H) ; 8.05 (mf : 1H) ; 8.27 (s : 2H).

Example 4:

(1*R*,2*S*,3*R*,5*S*)-3-{6-[1-(5-trifluoromethyl-pyridin-2-yl)-pyrrolidin-3(*S*)-ylamino]-purin-9-yl}-5-fluoromethyl-cyclopentane-1,2-diol, ^{1}H NMR (300 MHz, $(CD_3)_2SO$ d6, δ in ppm) : from 1.75 to 1.95 (mt : 1H) ; from 2.20 to 2.55 (mt : 4H) ; from 3.60 to 3.85 (mt : 3H) ; from 3.90 to 4.05 (mt : 2H) ; 4.37 (dd, J = 9 and 5.5 Hz : 1H) ; 4.55 (dd. J = 47.5 and 5.5 Hz : 2H) ; from 4.80 to 5.00 (mt : 2H) ; 6.79 (large d. J = 9 Hz : 1H) ; 7.93 (broad d. J = 9 Hz : 1H) ; 8.41 (broad s : 1H) ; 8.51 (mf : 1H) ; 8.69 (s : 1H) ; from 9.50 to 10.00 (mf : 1H).

Example 5:

(1*R*,2*S*,3*R*,5*S*)-3-{6-[1-cyclopent-1-ylamino]-purin-9-yl}-5-fluoromethyl-cyclopentane-1,2-diol

Example 6:

(1*R*,2*S*,3*R*,5*S*)-3-{6-[1-(5-chloro-pyridin-2-yl)-pyrrolidin-3(*S*)-ylamino]-purin-9-yl}-5-fluoromethyl-cyclopentane-1,2-diol. ^{1}H NMR (300 MHz. $(CD_3)_2SO$ d6. δ in ppm) : from 1.75 to 1.95 (mt : 1H) ; from 2.20 to 2.55 (mt : 4H) ; from 3.55 to 3.80 (mt : 3H) ; 3.92 (mt : 2H) ; 4.37 (dd. J = 9 and 6 Hz : 1H) ; 4.53 (dd. J = 47.5 and 5 Hz : 2H) ; 4.87 (mt : 1H) ; 4.96 (mf : 1H) ; 6.84 (large d. J = 8.5 Hz : 1H) ; 7.81 (broad d. J = 8.5 Hz : 1H) ; 8.13 (d. J = 2.5 Hz ; 1H) ; 8.50 (mf : 1H) ; 8.69 (s : 1H) ; from 9.40 to 10.00 (mfs : 1H).

Example 7:

(1*R*,2*S*,3*R*,5*S*)-3-{6-[1-(4-trifluoromethyl-phenyl-1-yl)-pyrrolidin-3(*S*)-ylamino]-purin-9-yl}-5-fluoromethyl-cyclopentane-1,2-diol, m.p.: 178°C

Example 8:

(1*R*,2*S*,3*R*,5*R*)-3-{6-[1-(5-trifluoromethyl-pyridin-2-yl)-pyrrolidin-3(*S*)-ylamino]-purin-9-yl}-5-trifluoromethoxymethyl-cyclopentane-1,2-diol, m.p.: 142°C

Example 9:

(1*R*,2*S*,3*R*,5*R*)-3-{6-[1-(5-chloro-pyridin-2-yl)-pyrrolidin-3(*S*)-ylamino]-purin-9-yl}-5-trifluoromethoxymethyl-cyclopentane-1,2-diol, m.p.:130°

Example 10:

(1*R*,2*S*,3*R*,5*R*)-3-{6-[1-(4-trifluoromethyl-phenyl-1-yl)-pyrrolidin-3(*S*)-ylamino]-purin-9-yl}-5-trifluoromethoxymethyl-cyclopentane-1,2-diol, m.p.: 153°

Example 11:

(1*R*,2*S*,3*R*,5*R*)-3-{6-[(*R*)-1-(3-chloro-thiophen-2-ylmethyl)-propylamino]-purin-9-yl}-5-trifluoromethoxymethyl-cyclopentane-1,2-diol, m.p.:140°

Example 12:

6-Chloro-9-((3a*S*,4*R*,6*R*,6a*R*)-6-difluoromethoxymethyl-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-yl)-9H-purine:

6-Chloroaristeromycine acetonide (5 g, 15.4 mmole), 8 g (122 mmole) zinc powder, and 10 g molecular sieves 3A° was stirred with 100 ml of dichloromethane at room temperature for 30 minutes. 4.5 g (15.4 mmole) $ZnBrCF_3x2$ CH_3CN was added and the resulting mixture was stirred overnight at room temperature. Additional 2.2 g (7.5 mmole) $ZnBrCF_3x2$ CH_3CN was added and the mixture was stirred an additional eight hours. Finally, another 2.2 g $ZnBrCF_3x2$ CH_3CN was added, and the mixture was heated at 50°C for five hours. The mixture was cooled to room temperature, dichloromethane was added

and the organic phase was washed with aqueous $NaHCO_3$. The organic layer was dried over MgSO4, filtered and concentrated in vacuo. The residue was chromatographically purified (silica; n-heptane/ethyl acetate 5/1) and yielded 6-chloro-9-((3a*S*,4*R*,6*R*,6a*R*)-6-difluoromethoxymethyl-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-yl)-9H-purine.

^1H NMR (500 MHz. ($CDCl_3$) δ in ppm) : 1.35 (s, 3H) ; 1.6 (s, 3H), 2.55 (m, 3H), 4.05 (m, 2H), 4.7 (m, 1H), 4.85 (m, 1H), 5.05 (m, 1H), 6.30 (t, 1H), 8.1 (s, 1H), 8.75 (s, 1H).This reaction was performed using a teflon apparatus.

Biological Data:

A.

Measurement of plasma lipdis (free fatty acids, triglycerides, cholesterol) in anaesthetized rats:

Plasma lipid levels were assayed in anaesthetized rats. Briefly, rats were anaesthetized with an intraperitoneal injection of pentobarbital sodium (60 mg/kg), tracheotomized, and one jugular vein per rat was cannulated for intravenous administration (bolus injection or infusion). Anesthesia was maintained for up to 7 hours by subcutaneous infusion of pentobarbital sodium (adjusted to the anesthetic depth of the individual animal; about 24 mg/kg/h). Body temperature was monitored with a rectal probe thermometer, and temperature was maintained at 37° C by means of a heated surgical plate. The rats were allowed to stabilize their blood levels after surgery for up to 2 hours, after which the test compound was injected intraperitoneally. Blood samples for glucose analysis (10 µl) were obtained from the tip of the tail every 15 minutes. For analysis of plasma lipids blood samples (0.3 ml) were obtained from the jugualr vein either every 10 to 15 minutes for up to 2 hours, or every hour for up to 5 hours after compound administration. Standard enzymatic procedures were used to determine blood glucose (Bergmeyer, 1974).

B.

Measurement of insulin sensitivity in conscious rats:

Insulin resistant Zucker Fatty rats or Zucker Diabetic Fatty (ZDF) rats were treated for up to 3 weeks with the test compound orally once daily. Plasma parameters were obtained by

E.

Antilipolytic effect in isolated rat adipocytes:

For the preparation of isolated rat adipocytes, epididymal fat pads were obtained from male Sprague-Dawley rats (150-180 g) killed by decapitation. The main fat pad blood vessel was removed with forceps and the pads were cut into small pieces. Digestion was carried out at 37°C in a shaking water bath by treating 1 g of sliced pad for 20 min with 3 ml of 1 mg/ml collagenase (type I, CLS, Worthington) in 1% BSA, fraction V, in KRH (Krebs-Ringer solution buffered with 25 mM HEPES/KOH, pH 7.4, containing 2.5 mM $CaCl_2$, 2 mM glucose, 1 mM sodium pyruvate, 0.5 units/ml adenosin deaminase and 200 nM phenylisopropyl adenosine). The adipocytes were filtered through nylon mesh of sufficient pore size that no pressure other than gentle teasing with a plastic spatula was necessary for the cells to pass through. After three cycles of centrifugation (500 g, 1 min), aspiration of the infranatant and resuspension in KRH containing 1% BSA, the cells were suspended in KRH containing 4% defatted BSA. Small aliquots of the final suspension were aspirated into capillary hematocrit tubes and centrifuged for 1 min in a Microhematocrit centrifuge in order to determine what fraction of the suspension consisted of fat cells. Results expressed as activities per unit volume of packed adipocytes (corresponding to equivalent numbers of cells) are based on this centrifugation procedure. Lipolysis was initiated by addition of a 100 µl aliquot of the adipocyte suspension to 700 µl of incubation medium [prewarmed to 37°C and consisting of KRH, 4% defatted BSA and 1 U/ml adenosine deaminase (type I, Sigma)], with or without addition of 8 µl of a solution of the appropriate test substance in 100% DMSO (at a concentration corresponding to 100 times its concentration in the final mixture). Thus, the final DMSO concentration in the incubation mixture was no greater than 1% and did not affect cell viability (as determined by the sensitivity of the adipocytes in respect of isoproterenol-induced lipolysis and its inhibition by insulin). Incubations were performed in 5 ml polypropylene vials agitated in a shaking water bath (140 cycles/min, amplitude 4.5 cm) at 37°C for 20, 40, and 60 min. The incubation was terminated by addition of 200 µl of 50 mM EDTA buffered to pH 7.4 with Tris. For the glycerol determination, the whole mixture was mixed rapidly and homogenized with a ground glass pestle in a 1 ml ground glass homogenizing tube (10 pulses). The homogenate was transferred immediately to a 1.5 ml Eppendorf cup

precooled to 4°C, after which the extracts were maintained at 4°C. The homogenate was then centrifuged (10,000 *g*, 15 min) and the infranatant below the fat cake removed with a glass Pasteur pipette, taking care not to aspirate the membrane pellet, and transferred to another Eppendorf cup. 300 µl aliquots of the infranatant were added to 300 µl volumes of 10% (w/v) $HClO_4$. The precipitate was in each case removed by centrifugation (10,000 *g*, 2 min) and the supernatant neutralized with 20% (w/v) KOH, followed by addition of 50 µl of 1 M Tris/HCl, pH 7.4, A 50 µl sample was then incubated (5 min, 37°C) with 1 ml of 0.1 M HEPES/KOH, pH 7.5, containing 2 mM ATP, 0.5 mM 4-aminoantipyrine, 1 mM EDTA, 0.5 U glycerol kinase, 4 U glycerol-3-phosphate oxidase, 2 U peroxidase, 2.7 mM *p*-chlorophenol, 0.04% Triton X-100 and 2 mM $MgSO_4 \cdot 7H_2O$, and the glycerol content determined from the absorbance at 505 nm. For the determination of free fatty acids, 300 µl aliquots of the incubation mixture were added to 3 ml of chloroform/heptane (1:1 v/v) containing 2% (v/v) methanol, and the liberated free fatty acids determined with copper reagent and bathocuproine. The inhibitory activities of the cyclipostins were calculated from the combined results (glycerol and free fatty acid release) by plotting the log of the dose against the percent response (with the adenosine deaminase-induced lipolysis set at 100%). Data in the linear portion of the log(dose)-percent response curves were analyzed using parallel-line bioassay techniques.

Antilipolytic effect:

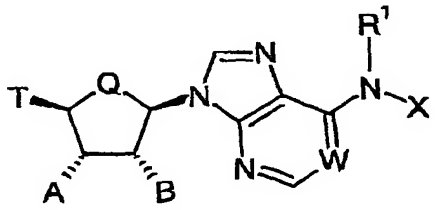
Example	IC_{50} *[nM]*
1	5
2	20
4	100
6	10
7	5
10	100

Aventis Pharma Deutschland GmbH

27. Juni 2002
APD61988EP IB/AEW/rg

Claims

1. A compound according to the general formula (I)



(I)

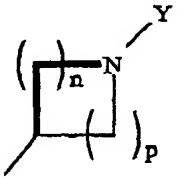
wherein:

W is N, N → O, or CH;

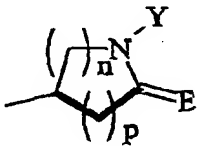
Q is CH_2 or O;

R^1 is selected from the group consisting of hydrogen, C_1-C_{10}-alkyl, allyl, 2-methylallyl, 2-butenyl and C_1-C_{10}-cycloalkyl;

X is selected from the group consisting of



;



;

wherein n and p are independently 0, 1, 2, or 3, provided that n + p is at least 1;

and unsubstituted and at least monosubstituted C_1-C_{10}-alkylene-Y, C_1-C_{10}-alkenylene-Y, C_3-C_{10}-cycloalkylene-Y and C_3-C_{10}-cycloalkenylene-Y, the substituents of which are

selected from the group consisting of halogens, pseudohalogens, CF_3, C_1-C_6-alkyl and C_1-C_6-alkoxy;

E is O or S;

Y is selected from the group consisting of hydrogen; and unsubstituted and at least monosubstituted C_1-C_{10}-alkyl, aryl, heterocyclyl, aryl-(C_1-C_{10}-alkylene)- and heterocyclyl-(C_1-C_{10}-alkylene), the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, aryl, heterocyclyl, C_1-C_6-alkoxy, NH_2, (C_1-C_6-alkyl)amino, di(C_1-C_6-alkyl)amino, C_1-C_6-alkoxy-(C_1-C_6-alkylene)-, nitro, carboxy, carbalkoxy, carboxy-(C_1-C_6-alkylene)-, carbalkoxy-(C_1-C_6-alkylene)-, hydroxy, hydroxy-(C_1-C_6-alkylene)-, mercapto, (C_1-C_6-alkyl)thio, mercapto-(C_1-C_6-alkylene)-, C_1-C_6-alkyl substituted by at least one halogen, (C_1-C_6-alkyl)sulfonyl-, aminosulfonyl-, (C_1-C_6-alkyl)aminosulfonyl-, (C_1-C_6-alkyl)sulfonylamido-, (C_1-C_6-alkyl)-sulfonyl-(C_1-C_6-alkylene)amino-, HO_3S-(C_1-C_6-alkylene)-, carbamoyl-(C_1-C_6-alkylene)-, (C_1-C_6-alkyl)-carbamoyl, (C_1-C_6-alkyl)-C(O)O-, (C_1-C_6-alkyl)-CO-,-SO_3H and carbamoyl;

T is a residue selected from the group consisting of C_1-C_{10}-alkyl, C_1-C_{10}-cycloalkyl, aryl-(C_1-C_{10}-alkylene)- and heterocyclyl-(C_1-C_{10}-alkylene), which residues are monosubstituted by halogen or OR_2, and which residues can be optionally substituted by at least one further substituent selected from the group consisting of halogens, pseudohalogens, mercapto, NH_2, nitro, hydroxy, unsubstituted and at least monosubstituted C_1-C_6-alkyl, C_1-C_6-alkoxy, (C_1-C_6-alkyl)amino, (C_1-C_6-alkyl)thio, aryl and heterocyclyl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy and hydroxy;

R^2 is C_1-C_{10}-alkyl substituted by at least one halogen;

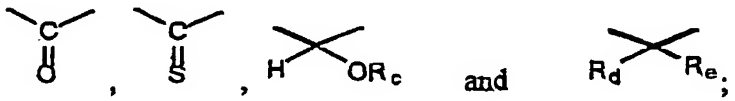
A is hydrogen, C_1-C_{10}-alkyl, hydroxy-(C_1-C_{10}-alkylene)-, C_1-C_{10}-alkoxy-(C_1-C_{10}-alkylene)-, or OR^c;

B ist hydrogen, C_1-C_{10}-alkyl, hydroxy-(C_1-C_{10}-alkylene)-, C_1-C_{10}-alkoxy-(C_1-C_{10}-alkylene)-, or OR^{cc};

R^c and R^{cc} are independently selected from the group consisting of hydrogen, C_1-C_6-alkyl,

aryl-(C_1-C_6-alkylene)-, (C_1-C_6-alkyl)-CO, carbalkoxy, aryl-(C_1-C_6-alkylene)-CO-, and aryl-O-CO-;

when A and B are OR' and OR'', respectively, R' and R'' together may form a substituent selected from the group consisting of



R_C is hydrogen or C_1-C_6-alkyl;

R_d and R_e are independently hydrogen, C_1-C_{10}-alkyl, or together with the carbon atom to which they are attached may form a 1,1-cycloalkyl group;

heterocyclyl is a 4 to 10-membered, mono- or bicyclic heterocycle containing one or more heteroatoms selected from the group consisting of N, O and S;

aryl is phenyl, indan-1-yl, indan-2-yl, naphth-1-yl or naphth-2-yl;

or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof;

with the proviso that, in case Q is O and Y is hydrogen, X is not C_3-C_6-cycloalkylene or C_3-C_6-cycloalkylene substituted by at least one halogen; in case Q is O and Y is hydrogen, C_1-C_{10}-alkyl or C_1-C_{10}-alkyl substituted by at least one hydroxy, X is not unsubstituted C_1-C_{10}-alkylene; in case Q is O and Y-X is 2-pyridin-4-yl-ethyl, T is not CF_3OCH_2-.

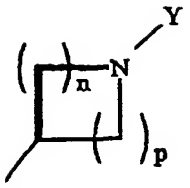
2. A compound according to claim 1, wherein in the formula (I)

W is N;

Q is CH_2;

R^1 is hydrogen or C_1-C_6-alkyl;

X is selected from the group consisting of



; and unsubstituted and at least monosubstituted C_1-C_{10}-alkylene-Y and C_3-C_{10}-cycloalkylene-Y, the substituents of which are selected from the group consisting of halogens, pseudohalogens, CF_3, C_1-C_6-alkyl and C_1-C_6-alkoxy;

n + p is 3 or 4;

Y is selected from the group consisting of hydrogen; and unsubstituted and at least monosubstituted C_1-C_{10}-alkyl, aryl and heterocyclyl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_6-alkyl, C_1-C_6-alkoxy, NH_2, (C_1-C_6-alkyl)amino, di(C_1-C_6-alkyl)amino, C_1-C_6-alkoxy-(C_1-C_6-alkylene)-, nitro, carboxy, carbalkoxy, hydroxy, hydroxy-(C_1-C_6-alkylene)-, mercapto, (C_1-C_6-alkyl)thio, mercapto-(C_1-C_6-alkylene)-, C_1-C_6-alkyl substituted by at least one halogen, (C_1-C_6-alkyl)sulfonyl-, aminosulfonyl-; (C_1-C_6-alkyl)aminosulfonyl-, (C_1-C_6-alkyl)sulfonylamido-, SO_3H and carbamoyl;

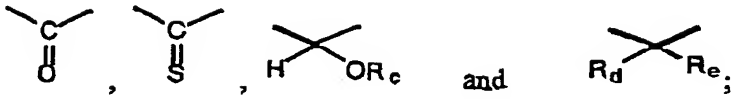
T is C_1-C_{10}-alkyl which is monosubstituted by halogen or OR^2, and which C_1-C_{10}-alkyl can furthermore be optionally substituted by at least one substituent selected from the group consisting of halogens, psendohalogens, mercapto, NH_2, nitro, hydroxy, unsubstituted and at least monosubstituted C_1-C_6-alkyl, C_1-C_6-alkoxy, (C_1-C_6-alkyl)amino, (C_1-C_6-alkyl)thio, aryl and heterocyclyl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy and hydroxy;

R^2 is C_1-C_{10}-alkyl substituted by at least one fluorine;

A is OR';

B is OR'';

R' and R'' are both hydrogen or R' and R'' together form a substituent selected from the group consisting of



R_c is hydrogen or methyl;

R_d and R_e are independently hydrogen, or C_1-C_6-alkyl;

heterocyclyl is selected from the group consisting of pyridyl, pyridazinyl, pyrimidinyl, isoquinolinyl, quinolinyl, quinazolinyl, imidazolyl, pyrrolyl, furanyl, thienyl, thiazolyl, benzothiazolyl, piperidinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, and morpholinyl;

aryl is phenyl, naphta-1-yl or naphtha-2-yl;

or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

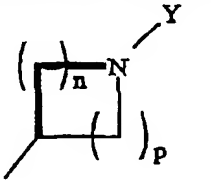
3. A compound according to claim 1 or 2, wherein in the formula (I)

W is N;

Q is CH_2;

R^1 is hydrogen;

X is selected from the group consisting of



and unsubstituted and at least monosubstituted C_1-C_6-alkylene-Y, the substituents of which are selected from the group consisting of CH_3, CH_3-CH_2, Cl, F, CF_3 and CH_3-O;

n + p is 3 or 4;

Y is selected from the group consisting of unsubstituted and at least monosubstituted aryl and heterocyclyl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy, NH_2, (C_1-C_3-alkyl)amino, di(C_1-C_3-alkyl)amino, C_1-C_3-alkoxy-(C_1-C_3-alkylene)-, nitro, carboxy, hydroxy, hydroxy-(C_1-C_3-alkylene)-, mercapto, (C_1-C_3-alkyl)thio, mercapto-(C_1-C_3-alkylene)-, and CF_3;

T is C_1-C_{10}-alkyl substituted by at least one substituent selected from the group consisting of halogen and OR^2;

R^2 is C_1-C_{10}-alkyl substituted by at least one fluorine;

A and B are both hydroxy;

heterocyclyl is selected from the group consisting of pyridyl, pyridazinyl, pyrimidinyl, imidazolyl, thienyl, thiazolyl, benzothiazolyl, piperidinyl, pyrrolidinyl, tetrahydrofuranyl, and morpholinyl;

aryl is phenyl;

or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

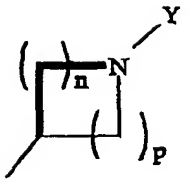
4. A compound according to any of the claims 1 to 3, wherein in the formula (I)

W is N;

Q is CH_2;

R^1 is hydrogen;

X is selected from the group consisting of



; and unsubstituted and at least monosubstituted C_1-C_6-alkylene-Y the substituents of which are selected from the group consisting of CH_3, CH_3-CH_2, Cl, F, CF_3 and CH_3-O;

n + p is 3 or 4;

Y is selected from the group consisting of unsubstituted and at least monosubstituted phenyl, pyridyl and thienyl, the substituents of which are selected from the group consisting of halogens, C_1-C_3-alkyl, C_1-C_3-alkoxy, hydroxy, mercapto and CF_3;

T is fluoromethyl, trifluoromethoxymethyl or difluoromethoxymethyl;

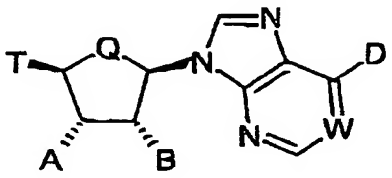
A and B are both hydroxy;

or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

5. A compound according to any of the claims 1 to 4, selected from the group consisting of:

(1R,2S,3R,5S)-3-{6-[1-(3-chloro-phenyl-1-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl}-5-fluoromethyl-cyclopentane-1,2-diol;
(1R,2S,3R,5S)-3-{6-[(R)-1-(3-chloro-thiophen-2-ylmethyl)-propylamino]-purin-9-yl}-5-fluoromethyl-cyclopentane-1,2-diol; and
(1R,2S,3R,5R)-3-{6-[1-(3-chloro-phenyl-1-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl}-5-trifluoromethoxymethyl-cyclopentane-1,2-diol;
or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

6. A compound according to the general formula (III)



(III)

wherein:

W is N, N → O, or CH;

Q is CH_2 or O;

D is halogen;

T is a residue selected fromt the group consisting of C_1-C_{10}-alkyl, C_1-C_{10}-cycloalkyl, aryl-(C_1-C_{10}-alkylene)- and heterocyclyl-(C_1-C_{10}-alkylene), which residues are monosubstituted by halogen or OR_2, and which residues can be optionally substituted by at least one substituent selected from the group consisting of halogens, psendohalogens, mercapto, NH_2, nitro, hydroxy, unsubstituted and at least monosubstituted C_1-C_6-alkyl, C_1-C_6-alkoxy, (C_1-C_6-alkyl)amino, aryl and heterocyclyl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy and hydroxy;

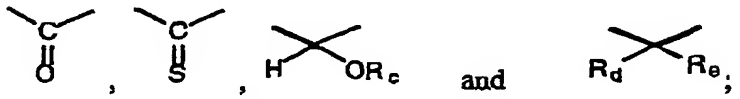
R^2 is selected from the group consisting of C_1-C_{10}-alkyl substituted by at least one substituent selected from halogens, C_1-C_6-alkyl-$S(O)_2$- and (C_1-C_6-alkyl)thio-C(S)-;

A is hydrogen, C_1-C_{10}-alkyl, hydroxy-(C_1-C_{10}-alkylene)-, C_1-C_{10}-alkoxy-(C_1-C_{10}-alkylene)-, or OR‘;

B ist hydrogen, C_1-C_{10}-alkyl, hydroxy-(C_1-C_{10}-alkylene)-, C_1-C_{10}-alkoxy-(C_1-C_{10}-alkylene)-, or OR‘‘;

R‘ and R‘‘ are independently selected from the group consisting of hydrogen, C_1-C_6-alkyl, aryl-(C_1-C_6-alkylene)-, (C_1-C_6-alkyl)-CO, carbalkoxy, aryl-(C_1-C_6-alkylene)-CO-, and aryl-O-CO-;

when A and B are OR‘and OR“, respectively, R‘ and R“ together may form a substituent selected from the group consisting of



R_C is hydrogen or C_1-C_6-alkyl;

R_d and R_e are independently hydrogen, C_1-C_{10}-alkyl, or together with the carbon atom to which they are attached may form a 1,1-cycloalkyl group;

heterocyclyl is a 4 to 10-membered, mono- or bicyclic heterocycle containing one or more heteroatoms selected from the group consisting of N, O and S;

aryl is phenyl, indan-1-yl, indan-2-yl, naphth-1-yl or naphth-2-yl;

or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

7. A compound according to claim 6, wherein in the formula (III)

W is N;

Q is CH_2;

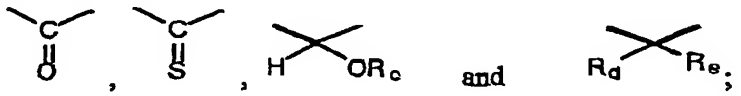
D is chlorine or fluorine;

T is fluoromethyl, trifluoromethoxymethyl, difluoromethoxymethyl, $CH_3SC(S)$-O-CH_2- or $CH_3S(O)_2$-O-CH_2- ;

A is OR‘;

B is $OR^{''}$;

$R^{'}$ and $R^{''}$ are hydrogen or $R^{'}$ and $R^{''}$ together form a substituent selected from the group consisting of



R_C is hydrogen or C_1-C_3-alkyl;

R_d and R_e are independently hydrogen or C_1-C_3-alkyl;

or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

8. A compound according to claim 6 or 7, selected from the group consisting of: 6-chloro-9-((3aS,4R,6S,6aR)-6-fluoromethyl-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-yl)-9H-purine; 6-fluoro-9-((3aS,4R,6S,6aR)-6-fluoromethyl-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-yl)-9H-purine; 6-chloro-9-((1R,2S,3R,5R)-5-fluoromethyl-1,2-dihydroxy-cyclopent-3-yl-)-9H-purine; 6-fluoro-9-((1R,2S,3R,5R)-5-fluoromethyl-1,2-dihydroxy-cyclopent-3-yl-)-9H-purine; 6-chloro-9-((3aS,4R,6S,6aR)-6-trifluoromethoxymethyl-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-yl)-9H-purine; 6-fluoro-9-((3aS,4R,6S,6aR)-6-trifluoromethoxymethyl-2,2-dimethyl-tetrahydrocyclopenta-1,3-dioxol-4-yl)-9H-purine; 6-chloro-9-((1R,2S,3R,5R)-5-trifluoromethoxy-methyl-1,2-dihydroxy-cyclopent-3-yl-)-9H-purine and 6-fluoro-9-((1R,2S,3R,5R)-5-trifluoromethoxymethyl-1,2-dihydroxy-cyclopent-3-yl-)-9H-purine, or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

9. A compound of the general formula (I) according to any of claims 1 to 5 or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof, for use as a pharmaceutical.

10. The use of a compound as defined in any of claims 1 to 5 or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof for the manufacture of a medicament for the

treatment of insulin resistance, type 2 diabetes, metabolic syndrome, lipid disorders or cardiovasular disease or for providing an anti-lipolytic effect.

11. The use according to claim 10 for the manufacture of a medicament for the treatment of insulin resistance or type 2 diabetes.

12. A pharmaceutical preparation comprising a pharmaceutically acceptable carrier and an effective dose of at least one compound of the formula (I) as defined in any of claims 1 to 5 or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

13. A pharmaceutical preparation according to claim 12, which pharmaceutical preparation is in the form of a pill, tablet, lacquered tablet, sugar-coated tablet, suckable tablet, granule, capsule, hard or soft gelatin capsule, aqueous, alcoholic or oily solution, syrup, emulsion or suspension, suppository, solution for injection or infusion, ointment, tincture, cream, lotion, powder, spray, transdermal therapeutic systems, nasal spray, aerosol mixture, microcapsule, implant, rod or plaster.

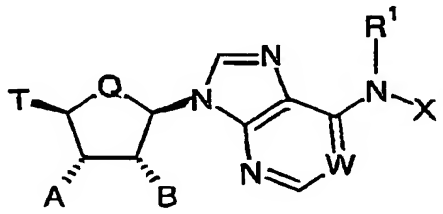
14. A method for the synthesis of a compound according to any of claims 1 to 5 which method comprises reacting the respective 6-chloropurine and/or 6-fluoropurine with an appropriate amine, optionally followed by a functionalization of the thus-obtained compound.

Aventis Pharma Deutschland GmbH

27. Juni 2002
APD61988EP IB/AEW/

Abstract

The present invention relates to compounds according to the general formula (I)



(I)

wherein R^1, A, B, Q, T, W and X have the meanings given in the description.

These compounds are useful for the manufacture of a medicament for the treatment of insulin resistance, type 2 diabetes, metabolic syndrome, lipid disorders or cardiovasular disease or for providing an anti-lipolytic effect.